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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

DECEMBER, 1935

ORIGINAL ARTICLES.

URINE FORMATION IN THE AMPHIBIAN KIDNEY.*

By A. N. Richards, Ph.D.,
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It has been known for some 60 years that the frog's kidney offers opportunities to the physiologic experimenter which are not afforded by the more compact, inaccessible and intricate mammalian kidney. The first practical recognition of these opportunities was made by Nussbaum[2] who, in 1878, showed that the double blood supply of the frog's kidney might make possible the separate study of the functions of the glomerulus and of the tubule. He ligated the renal arteries, leaving the capillary circulation of the tubules by way of the renal portal vein intact; found that after injection of urea urine was formed and concluded therefore that the epithelium of the tubules contains a secretory mechanism. This famous experiment, refined by Beddard and Bainbridge,[3] seemingly unambiguous, has formed one of the firmest supports of the doctrine of secretion by the tubule.

Thirty years later Cullis[4] utilized the double circulation of the frog's kidney in a somewhat different way by inventing the method of double perfusion. Inserting one cannula into the aorta and another into the renal portal vein or its collateral, the anterior abdominal vein, she showed the possibility of presenting to the tubule of the surviving kidney substances which were not contained in the fluid which was perfused through the glomeruli. This

* A lecture delivered before the Harvey Society by A. N. Richards, January 17, 1935.

method, subsequently perfected, has been widely adopted particularly in the study of problems of secretion by the renal tubule.

The development of another method for which the frog's kidney, because of its translucency is particularly suited, began in 1920 when, in Leonard Hill's laboratory in London[5] and in our laboratory in Philadelphia,[6] this structure was subjected to microscopic study during life. Hill's problem was that of the blood pressure in the glomerular capillaries; ours, the behavior of the glomerular circulation during the action of minute concentrations of adrenalin. Hill confined his study of this preparation to his original problem. In our laboratory a plan developed to attempt the withdrawal by capillary pipettes of fluid from single renal units at different levels of the nephron in the hope that chemical tests or analyses might yield a description of urine at various stages in its elaboration.* Such a plan, if realized, would, it was thought, tell us unequivocally whether glomerular fluid has the composition of a filtrate or whether it is the product of selective secretion; whether processes of reabsorption or secretion or both are operative within the tubule and in what parts of the tubule they occur. Such information in turn might conceivably lead to identification of the means whereby the renal mechanisms are regulated and adjusted to meet the excretory requirements of the body.

In the execution of this plan the first point of attack chosen was the glomerulus, partly because of its size and accessibility; partly also because of the conviction that from the standpoint of orderly experimentation with the kidney it is the most important. So much of our thinking concerning events which take place in the tubule depends for its soundness and fertility upon correct information concerning the volume and character of glomerular excretion that no amount of effort seemed too great if this could be secured.

It was relatively easy to construct a simple apparatus, the essential item of which is a sharply pointed micropipette, with which Bowman's capsule could be punctured and minute amounts of fluid withdrawn. Nor was it excessively difficult to transfer such collected fluids to capillary tubes and to subject them to qualitative tests for various constituents. The results were in general accord with the postulates of the filtration theory of glomerular function, *i. e.*, the glomerular fluid was found not to contain protein, it was alkalin, contained urea, chlorid, reducing substance, potassium, and certain dyes, if these had been injected before the experiment was begun.[7] These results, first obtained with glomerular urine from the frog, were confirmed a little later by White and Schmitt[8] with glomerular fluid similarly obtained from Necturus.

This demonstrated qualitative resemblance between the glom-

* In the initiation and early development of this plan the collaboration of Dr. J. T. Wearn was most important. Later developments have been greatly assisted by generous financial support from the Commonwealth Fund.

erular fluid and a protein-free plasma filtrate was scarcely adequate to decide the questions which concerned us; quantitative information was necessary; and in getting this, genuine difficulties were encountered because of the minute quantities of fluid available for analysis. To be useful in this connection a quantitative method must be applicable to a volume of fluid of the order of 0.5 cmm. or even less; and in the handling of these quantities of fluid rigid precautions must be adopted against contamination and evaporation. Successful adaptation of existing methods to these requirements has been accomplished which makes possible the following quantitative determinations on from 0.1 to 0.5 cmm. of fluid: total molecular concentration, total electrolytes (electrical conductivity), chlorids, inorganic phosphate, glucose, urea, uric acid, creatinin, pH, and the dyes: phenol red, neutral red and indigo carmine. Each method was tested rigorously by analyses of pure solutions and its accuracy approximately defined.

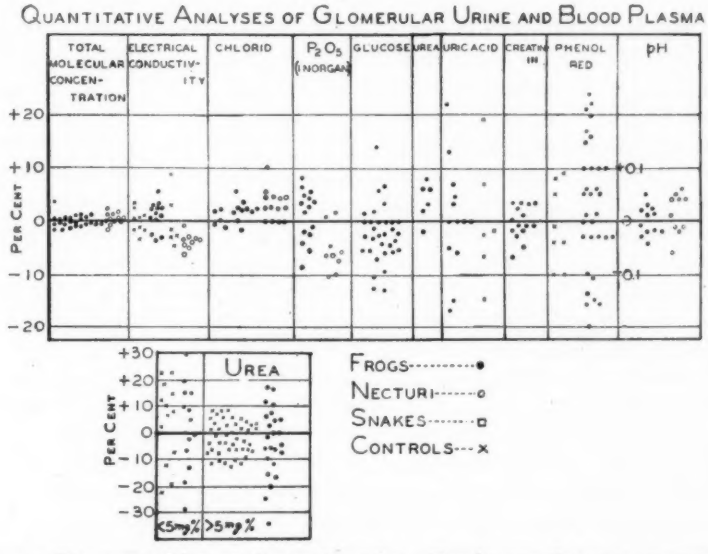

FIG. 1.—The composition of glomerular urine. Results are shown as percentage differences from blood plasma or an ultrafiltrate from it.

Assembled on a single chart (Fig. 1) are the results which have been obtained by applying these methods in quantitative comparisons of the composition of glomerular urine and blood plasma. It includes work with the 2 species, frog and Necturi and a few estimations of uric acid in glomerular urine of snakes. Each circle on the chart represents the result of a quantitative analysis of glomerular urine. Its position above or below the abscissa shows its percentage deviation from the corresponding value in plasma or in an ultrafiltrate from plasma.

The first section shows results of 32 comparisons[9] of the total concentration of glomerular urine and plasma from the same animal, obtained by Barger's method as adapted by H. L. White[10] for the purpose of this study. Omitted are White's earliest figures which he now regards as erroneous. In almost every case the correspondence represents identity. The results show that in frogs and Necturi the total concentration of glomerular urine and of blood plasma are the same, the osmotic pressure being approximately equal to that of a 0.6% solution of NaCl.

The second section shows that the total electrolyte content of the two fluids is the same.[11] The third shows that the Cl concentration of glomerular urine is on the average slightly higher than that of plasma.[12] The difference is within the errors of method, but the consistency of its sign indicates that it is not fortuitous. It may be explained by a Donnan equilibrium at the glomerular membrane. Omitted are earlier determinations by Wearn and Richards[13] and by Freeman, Livingston and Richards[14] by the nephelometric method now regarded as unreliable. Included are five determinations by Ekehorn[15] made by microtitration according to Mohr; the others were made by Westfall and Findley in our laboratory by a recently devised development of Isaacs' colorimetric method, found to be exceedingly sensitive and reliable.

Inorganic phosphates,[16] glucose,[17] uric acid[18] and creatinin[19] were determined by capillary tube adaptations of the methods of Kuttner, Sumner and Folin. The approximately equal distribution above or below the abscissa, the fact that the majority of the figures fall within the average errors of the methods are evidence of identity of concentration of each of these constituents in glomerular urine and plasma.

Concentration of phenol red was determined by simple capillary tube colorimetry.[20] Glomerular urine and plasma from a frog previously injected with the dye were made alkalin with NH_3 vapor and intensity of color determined by comparison with standard solutions. Only from 60 to 90% (average, 71) of phenol red in frog's plasma is uncombined with protein and hence filterable. In each case, therefore, 71% of the total phenol red concentration of plasma was taken as the value with which to compare the concentration of phenol red in glomerular urine. The approximately equal distribution of the points above and below the abscissa is regarded as evidence of the probability that had the correction for combined phenol red in plasma been accurately known in each experiment, values of phenol red in glomerular urine and plasma ultrafiltrate would have been more nearly coincident.

pH was determined by Dr. Montgomery[21] by collecting in quartz capillary tubes glomerular urine from animals previously injected with phenol red, due precautions against loss of CO_2 being taken. Color comparisons were made with standard buffer solutions in

quartz capillary tubes containing approximately the same concentration of phenol red as the glomerular urine.

The urea estimations constitute one of the most important sections of the chart. Only 6 are included, despite the fact that more than 40 other experiments have been made. The reason for this is that the analytical method[22] has recently been refined and these 6 experiments are the only ones which have since been made. In a separate section are shown the earlier results. The crosses represent each the result of a microanalysis of a known solution, not known to the analyst. Its position with reference to the abscissa represents the percentage difference between the concentration known and the concentration found. The black circles represent similar microdeterminations of urea in glomerular urine, placed on the chart so as to show percentage difference from urea in the plasma. The first section includes determinations on solutions and samples of glomerular urine in which the concentration was less than 5 mg. N per 100 cc. The second from 5 to 20 mg. per 100 cc. If it is considered that only 1 analysis is required to define the position of a cross, while 2 analyses (1 of glomerular urine and 1 of plasma) are required to give the position of each circle, the greater spread of the circles is understandable. These figures indicate even more convincingly than do the 6 values in the larger chart that the concentration of urea in glomerular urine is the same as that of plasma.

The only conclusion which seems to emerge from this assemblage of data is that glomerular urine has the composition of an ultrafiltrate from plasma; that were the glomerular membrane a structure which could either selectively retard or selectively accelerate the passage of a diffusible constituent of the plasma through it, in some one of the categories represented in this chart a trend of difference between glomerular urine and plasma would be evident. Such a trend is seen in the chlorids, but it is in the direction and its magnitude is of the order which was predicted from our knowlege of the Donnan membrane equilibrium. The conclusion is that this fairly extensive study reveals nothing which indicates that the glomerulus is capable of secreting.

Before citing some further information which confirms and amplifies that already given, it seems necessary to interject two statements, the omission of which would constitute a serious gap in the argument. First concerning blood pressures: If the pressure within the glomerular capillaries is insufficient to overcome the resistance to filtration which the osmotic pressure of the plasma proteins presents, the conclusion that the glomerular process is solely one of filtration would be absurd. The first measurements of glomerular capillary pressure, made by Leonard Hill and McQueen in 1921,[5] seemed to make it highly questionable that an effective filtration pressure exists in the glomerular capillaries. However, two sub-

sequent examinations of this question have been made, one by Hayman,[23] the other by White[24] by a method more direct and believed to be more trustworthy. The results were as follows:

	H_2O, cm.	Average.
FROGS. (HAYMAN.)		
Glomerular capillary pressure	10.0 to 27.0	20.2
Plasma colloid osmotic pressure (Churchill, Nakazawa and Drinker)	1.5 to 13.4	5.3
Filtration pressure	8.5 to 13.6	14.9
NECTURUS. (WHITE.)		
Glomerular capillary pressure	8.5 to 27.0	17.7
Plasma colloid osmotic pressure	6.5 to 14.2	10.4
	2.0 to 12.8	7.3
Intracapsular pressure	0.1 to 2.8	1.5
Effective filtration pressure	1.9 to 10.0	5.8

From these figures we conclude that the blood pressure in the glomerular capillaries is amply sufficient to effect the separation of a protein-free fluid from the blood passing through them.

Second, we must meet the possible criticism that failure to find evidence of a secretory process is due to injury produced by the experimental conditions. The animals (frogs) as a rule are immobilized not by an anesthetic but by destruction of the brain. In opening the abdomen and arranging the kidney for observation, the kidney itself is not touched by instruments and not directly exposed until the puncture is about to be made. The general circulation and the renal circulation is vigorous; when it is not, collection of fluid is impossible. The glomerulus itself is protected by the peritoneum and the capsule of Bowman; its vessels are bathed inside by flowing blood, outside by continually renewed glomerular fluid. Puncture of the capsule can be and usually was accomplished without touching the capillaries of tuft with the tip of the pipette; suction was not used in the great majority of instances in collecting the fluid; reflux from the tubule was prevented by blocking the neck of the tubule by gentle pressure with a microscopic glass rod. We think that despite the necessary mutilation of the animal there is little reason to suspect any consistent direct injury to the glomerular structures.

The further information to which allusion was made a moment ago concerns the glomerular excretion of 4 additional foreign substances after their subcutaneous or intravenous injection. Two of these, indigo carmine and ferric ammonium citrate, are substances the glomerular excretion of which has been denied by those who have studied fixed sections of the kidney excised during their excretion.[25] One has only to look at the kidney of a frog during the few moments immediately following the intravenous injection of

indigo carmine to be convinced that it escapes into the capsule of Bowman of every glomerulus through which blood is vigorously flowing. Color comparisons of glomerular urine with known solutions of indigo carmine indicate that its concentration in glomerular urine is approximately the same as that of uncombined indigo carmine in the plasma. These comparisons have not the degree of accuracy of the other determinations listed, hence were not included in the chart.

In each of 10 experiments made by Dr. John Reisinger in which frogs were injected with ferric ammonium citrate, iron was identified in the collected glomerular urine. In 6 experiments in which the kidneys were perfused by way of the aorta with Ringer's solution containing this substance, the concentration of iron in the glomerular fluid was approximately the same as that in the perfusion fluid. The reason why quantitative figures are not given is that we have not yet succeeded in determining the uncombined, filterable iron in plasma. From these facts we believe that the histologic method as it has been applied in the past to the study of the glomerular elimination of these substances has given misleading results.

Neutral red is another substance of interest in this connection. Perfused in Ringer's solution through the frog's renal arteries, it passes into glomerular fluid in the same concentration as in the perfusion fluid. Injected intravenously, scarcely detectable traces can be found in glomerular urine. The reason is that it is almost wholly combined with plasma proteins and hence, except in traces, does not pass through a membrane impermeable to protein.

The fourth substance, inulin, is in a different category from any thus far mentioned. This polysaccharid is non-toxic and can be injected intravenously in large amounts. Its peculiar interest arises from its high molecular weight, and, it is to be assumed, its great molecular size. Haworth estimated its molecular weight at 5000;[26] Irvine at about 3800.[27] It is thought to consist of an open chain of 29 or 30 levulose units. It is not hydrolyzed by enzymes of the animal body and after intravenous injection in mammals is quantitatively excreted unchanged in the urine. It was found in a series of preliminary experiments that when injected into frogs or perfused through the arteries of a frog's kidney the glomerular fluid contained it in the same concentration as that in which it existed in the blood or perfusion fluid. The glomerular membrane permits the inulin to pass through it as completely and apparently as readily as urea or creatinin.

By testing the filterability of inulin through artificial membranes we have tried to arrive at a more concrete description of the glomerular membrane. The membranes used were collodion, prepared according to Greenberg and Gunther,[28] and DuPont's Cellophane 450 and 600. Through the collodion membrane, inulin, creatinin and NaCl were equally filterable; *i. e.*, the concentration of each in

the filtrate was the same as in the original fluid. Cellophane 450 allowed only 30% of the inulin to pass through; cellophane 600, only 16%; both, however, allowed creatinin and NaCl to pass through in their original concentrations.

If we conceive the passage of fluid and solute through the glomerular membrane to take place through pores in it, we may conclude that these pores resemble in size those of the collodion membrane and are larger than the majority of those in cellophane.

From these results with inulin it may be argued that the glomerular membrane, which permits the filtration of a substance of such large molecular dimensions as may presumably be ascribed to inulin must, *a fortiori*, permit free filtration of the far smaller molecules of the normal urinary constituents. This argument adds support to the conclusion drawn from the analytical data. It is similar to one put forward 4 years ago by Ekehorn,[1] based partially upon the fact that in his experience glomerular fluid collected from frogs usually contained large amounts of protein. In essence he says: If in the glomerular membrane there are holes large enough to permit escape of the huge molecules of protein, that membrane can be nothing else than a sieve for such small molecules as those of urea, etc. Our experience concerning protein in the glomerular fluid differs from that of Ekehorn. The glomerular fluid from normal animals contains no protein or only traces. By traces is meant from 5 to 20 mg. per 100 cc. These minute amounts of protein have been shown by Dr. Queen in our laboratory to be almost invariably mixtures of albumin and globulin. This seems to mean that here and there in the glomerular membrane, with its myriads of pores, each large enough to permit the passage of inulin molecules, there may be found a few defects large enough to allow whole plasma to pass through; the escape of protein through these does not carry any such implication concerning the character of the normal membrane, or the normal parts of the membrane, as does the fact of the complete glomerular filterability of inulin through the entire membrane.

From the facts and considerations which have thus far been presented we conclude that the glomerulus of the amphibian kidney is a filter and not a secreting structure.

How does the volume of glomerular filtrate compare with the volume of urine which the kidney excretes? From a single glomerulus of the exposed kidney of a frog we frequently obtain filtrate at a rate of 1 cmm. per hour. On several occasions collections have been made at rates of from 3 to 4 cmm. per hour. In the normal, wet, unmolested frog we may believe that the filtration rates are higher rather than lower than these. When these rates are used in calculating the total glomerular filtrate formed per hour by the kidneys of a grass frog each of which contains 2000 glomeruli, the estimated filtration rate is from 4 to 16 cc. per hour. The higher

figure is about 8 times as great as the maximum urine output of similar frogs under normal conditions and the lower figure is from 10 to 20 times as great as the urine output of operated frogs.

Is the volume of the glomerular filtrate sufficient to contain all of the substances which the kidney excretes? In our experience, limited in this connection, neutral red is the only substance studied in the renal excretion of which we have been obliged to assume the participation of another mechanism than that of glomerular filtration. From figures for the amount of neutral red excreted per hour, its concentration in the glomerular urine and the number of glomeruli in the kidney it was calculated that from 20 to 57 cmm. of filtrate per glomerulus per hour would have been required to contain the excreted dye. We do not believe that rates as high as these are possible. Hence we conclude that a large fraction of the neutral red was excreted by the tubules. Similar calculations from figures for phenol red indicated that all of this dye which was excreted might have been contained in the glomerular filtrate. These results agree with conclusions drawn from Oliver and Shevky[29] from perfusion experiments.

Similar calculations can be made from data of Marshall and Crane[30] concerning the excretion of urea and phenol red in frogs. In the great majority of cases, the calculated rates of filtration were less than 5 cmm. per glomerulus per hour, and hence do not require the assumption that the tubule secretes these substances. Marshall, however, on the basis of high concentration ratios, higher concentration in kidney tissue than in blood and comparisons with the excretion rate of xylose, believes that they are in large part secreted by the frog's tubule. We think that the force of this evidence is far less than that which he has brought forward showing that phenol red is secreted by the tubules of the dog's kidney.[31]

The question may now be asked whether the conclusion, drawn from direct evidence obtained in amphibia, that the glomerular process is solely one of filtration, is applicable to the mammalian kidney, from which as yet no such direct information has been obtained. We believe that it is.

Careful comparisons of structure, made with the aid of modern histologic methods, reveal no difference which suggests that the mammalian glomerulus is a secretory apparatus. On the contrary, the epithelial investment, particularly the epithelial nuclei, are more conspicuous in the glomeruli of amphibia than in those of mammals.

It is unnecessary to review the mass of older evidence, chiefly indirect, which has led the majority of physiologists to accept the filtration doctrine. We wish, however, to add to this evidence some recent observations of our own which have greatly strengthened our conviction in this regard. They concern the excretion of inulin by the dog's kidney.

Inulin has already been described as a polysaccharid of molecular

weight of the order of 3800 to 5000 and presumably of large molecular dimensions. It is not hydrolyzed in the animal body and has been demonstrated to be filterable through the frog's glomerulus. Injected intravenously into a toadfish it is not excreted in the urine, *i. e.*, it is not secreted by the tubule of the aglomerular kidney. The frog's kidney is unable to excrete it when, in a double perfusion experiment, it is contained in the fluid which flows through the intertubular capillaries but not in that flowing through the glomerular capillaries. When injected intravenously into a dog it is excreted quantitatively in the urine with astounding rapidity and often in concentrations amazingly high.[32] For example in one dog, 14.5 gm. was injected intravenously. Urine passed in the following 11 minutes contained 5.5 gm. (38% of the injected dose). In the 43 minutes following the end of the injection the kidneys had excreted 10.2 gm. (70%). In several experiments the concentration of inulin in the urine has been found to be as high as 36%.

To prove that this remarkable performance is the result of glomerular filtration solely, it is necessary to show that the tubules of the dog's kidney do not secrete it into their lumina. To get evidence concerning this we have used the classical experiment of Heidenhain which has been one of the chief bulwarks of belief in tubular secretion. A dog's blood pressure was reduced by section of the spinal cord to a level of 30 mm., *i. e.*, a level at which glomerular filtration may be believed to have ceased. Inulin was then injected intravenously. After 20 minutes, during which blood pressure did not rise above 35 mm., the vessels of one kidney were perfused, first with some of the dog's own blood, taken before the inulin injection, in order to wash out the inulin-containing blood, then with warm oxygenated Locke's solution for the few minutes required to get a small amount (0.5 cc.) of urine from its ureter. This urine contained no detectable trace of inulin. Analysis of the cortex of the kidney showed that the concentration of inulin in it was far lower than that in the blood plasma. These results, absence of inulin from urine and low concentration in kidney tissue, give evidence that the low blood pressure prevented glomerular filtration and that no inulin was secreted by the tubules. That the tubules during that period were capable of secreting was shown by the behavior of phenol red which was injected intravenously along with the inulin. The cortex contained the dye in concentration nearly double that of the plasma and the urine obtained by perfusion of the kidney after its excision contained significant amounts.

If the conclusion drawn from these experiments is true, namely, that in the dog the glomerulus is the sole renal pathway of escape of inulin from the blood, it follows from the rapidity with which it is excreted that the volume of the glomerular filtrate is vastly greater than that of the urine which leaves the kidney. In one experiment on a dog weighing 17.5 kg., the volume of glomerular

filtrate calculated from the plasma and urine concentrations and the amount of inulin excreted per minute varied between 84 and 114 cc. per minute. The corresponding rates of urine excretion were 1.8 and 5 cc. per minute. From these figures and Kunkel's estimates of the number of glomeruli in the dog's kidney[33] it was calculated that 5 to 7 cmm. of filtrate per glomerulus per hour were formed. These figures are easily credible when it is recalled that as much as 4 cmm. per hour have been collected from a single frog's glomerulus.

Another substance the excretion of which has long been employed in similar calculations of the rate of glomerular filtration in mammals is creatinin. Rehberg,[34] in 1926, accepting Cushny's hypothesis that all of the normal constituents of urine are separated from the blood by glomerular filtration only, chose creatinin, the concentration of which in urine is highest relative to plasma, as the substance whose rate of excretion would most truthfully show the volume of glomerular filtration. If the validity of his assumptions is granted, the amount of creatinin excreted per minute divided by the amount contained in 1 cc. of plasma should give the number of cubic centimeters of glomerular filtrate per minute; and if our conclusion with respect to inulin is correct the results of the calculations from the excretion of creatinin and of inulin should be the same. In a series of experiments with dogs, inulin and creatinin were injected simultaneously.[32] Calculations of the glomerular filtration rate from the urine and plasma values of each substance gave approximately the same value. On the average the plasma clearance of inulin was about 10% higher than that of creatinin. The inference from this is that in the dog both inulin and creatinin leave the blood by filtration but that a little creatinin goes back into the blood as the filtrate flows down the tubule.*

In 1932 Jolliffe, Shannon and Smith[35] proposed that the plasma clearance of the non-metabolized sugar, xylose, is a more correct measure of glomerular filtration in mammals than that of creatinin. The reasons for the preference lay in the fact that creatinin is excreted by the tubule of the aglomerular fish while xylose is not and in the belief that xylose cannot be reabsorbed from the renal

* Our experiments with inulin were begun in March, 1933, as the result of the desire to find a substance which would not escape from the lumen of the tubule either by active reabsorption or passive diffusion. It soon became obvious that a study of its excretion by mammals might throw light on the question of the indirect measurement of glomerular filtration in mammals and accordingly the experiments with dogs were begun. In October, 1934, we learned that Professor Homer W. Smith and Dr. James F. Shannon had independently inaugurated work with this substance at about the same time and had completed a series of studies more extensive than ours. Their experiments with dogs showed even more consistently than ours that the clearance of inulin is the same as that of creatinin and greater than that of xylose. It is a pleasure to acknowledge the help which we have since received from conversations with Professor Smith and improvements in technique of our experiments which Dr. Shannon assisted us in making. The results which they have obtained in dogs are published in the American Journal of Physiology, **112**, 405, 1935.

tubule. Their work with xylose led to the conclusion that a considerable fraction of creatinin is secreted from the blood into the tubule and hence that its excretion does not give a valid measure of glomerular function. Our finding that inulin clearance is the same or greater than that of creatinin and decidedly greater than that of xylose gives reason for belief that xylose is reabsorbed from the tubule; that less of it is excreted by the kidney than is filtered from the blood in the glomeruli.

Study of the excretion of inulin and creatinin by the dog has yielded information which affords an interesting comparison of the function of glomerular capillaries with that of the systemic capillaries. In the experiment cited in which 14.5 gm. of inulin were injected intravenously, 38% of this was excreted in 11 minutes; another 32.5% in the following 32 minutes. Two and four-tenths grams of creatinin were simultaneously injected. Only 16% was excreted in the first 11 minutes, and 17% in the next 32 minutes; yet the plasma was being cleared of the two substances at approximately the same rate. This difference in the rates of actual excretion by the kidney is due to the fact that a much greater fraction of the injected creatinin than of the injected inulin passed out of the blood into the tissues. As has been stated, when a solution of inulin and creatinin is filtered through a collodion membrane with pressure, both substances pass through at the same rate; but when a solution of the two is dialyzed through collodion, it is found that creatinin passes through faster than inulin. From this it is clear that in the dog while inulin and creatinin were passing through the walls of the glomerular capillaries at approximately the same rate in relation to their concentrations in the plasma, creatinin was moving through the walls of the systemic capillaries faster than inulin. This is, of course, what is to be expected if, as we believe, the glomerular process is purely one of filtration while that in the systemic capillaries is a combination of filtration and diffusion.

Changes Which the Glomerular Filtrate Undergoes in Its Passage Through the Tubule.* The methods developed for the collection and analysis of glomerular fluid have proved to be applicable to the study of tubular fluid. Tubules have been punctured at various levels, the sites of puncture being identified either by observation of the kidney during life or after its excision at the end of an experiment. In the latter case the lumen of the punctured tubule was filled with India ink, the kidney immediately excised and dehydrated. After clearing, a scale drawing of the ink-injected tubule was made, and the distances of puncture hole from the ends of the section

* The results outlined in this section have not yet been published in detail. The experiments on the reaction of tubule fluid were made by Drs. Hugh Montgomery and J. A. Pierce; the others were made in collaboration with Drs. C. L. Hudson, T. P. Findley and J. P. Hendrix. Abstracts may be found in the American Journal of Physiology (Proceedings), **109**, 63, 76, 87, 107, 1934.

of the tubule in which it was found were measured.* Thus, in many experiments the distance within the lumen of the tubule which had been traversed by the fluid before it was collected was accurately known; in the others it was approximately known.

The manipulative difficulties are greater than in glomerular puncture and collection of glomerular urine. This is particularly true in work with the frog's tubule because of its small size, its great tortuosity and because of the difficulty of distinguishing between the proximal and distal convolutions in the living tissue. For this reason the greater number of experiments have been made with Necturi in which the tubule is larger and less complex in arrangement.

It was obviously important not to draw fluid into the collecting pipette from parts of the tubule distal to the site of puncture. This mistake was avoided by injecting a globule of mercury or of mineral oil colored with Scharlach R in such a way that the lumen of the tubule was obstructed by it at a point immediately distal to the point of the pipette.

In one group of experiments it was desired to introduce into the tubule an artificial fluid of known composition at one point; take it out for analysis at another. Omission of one plasma constituent from the fluid made it possible to learn whether or not that constituent can come in from the blood; addition of it in excess made it possible to learn whether it was reabsorbed into the blood.

The fashion in which such perfusions of the lumina of single tubules were accomplished can be illustrated by describing the method of perfusing a proximal tubule in Necturus. Enough metallic mercury was injected into a renal corpuscle to fill the capsular space, the neck and about 0.5 mm. of the beginning of the proximal tubule. This abolished glomerular filtration. The pipette was then filled with the perfusion fluid and its tip inserted into the lumen of the mercury-filled portion of the tubule. Injection of a little fluid caused the mercury column to break and a globule of mercury to be driven to the distal end where it was arrested by the narrowness of the intermediate section. Injection was interrupted and a second pipette inserted at a point proximal to the mercury blocking the distal end. Fluid from the first pipette was then allowed to flow through the tubule at a slow rate and was collected in the second pipette.

The experiments thus far undertaken concern the reabsorption of water, chlorid and glucose, the change in reaction and changes in the concentrations of inorganic phosphates, urea, uric acid and creatinin. The task has been to measure the changes and to identify the parts of the tubule in which they occur. In every experiment blood was collected at nearly the same time as the tubule fluid and the plasma analyzed along with this. On the basis of the

* These identifications were made by Dr. R. T. Kempton.

analyses of glomerular urine presented above, it is assumed throughout that the concentration of any constituent studied is the same in plasma and in the glomerular filtrate from it. In the accompanying charts the results are plotted as percentage differences between plasma and tubule fluid.

1. *Water.* The discrepancy between the volume of urine which leaves the kidney and the volume of the glomerular filtrate, calculated from the amount of fluid which can be collected from a single glomerulus, is such as to give presumptive evidence of the reabsorption of a large fraction of the glomerular filtrate as it passes through the tubule. More direct evidence of water reabsorption has been obtained by observing the increase in intensity of color which takes place in a phenol red solution injected into and allowed to remain in a single tubule of the frog's kidney. In this experiment the chief site of water reabsorption appeared to be the proximal part of the distal tubule. Some, however, of the water which is reabsorbed passes out through the wall of the proximal tubule. This is shown by the greater difficulty which is encountered in collecting fluid in volume sufficient for analysis from the distal end of the proximal tubule than from the glomerulus or levels of the tubule nearer to it. It is also shown by the observation that when Ringer's fluid was perfused through the lumen of a proximal tubule at a rate and pressure comparable to those of a normal glomerular fluid, the amount collected was significantly less than the amount introduced. Further evidence in this category will be found in the figures for concentration of glucose in fluid collected from proximal tubules of animals poisoned with phlorhizin.

Concerning the possible secretion of fluid into the proximal tubule it can be said as the result of several trials that in Necturus, after glomerular filtration had been purposely abolished, attempts to collect fluid from the proximal tubule failed.

2. *Total Concentration; Chlorid Concentration.* The results shown graphically in Figure 2 prove that the activities of the tubule which are responsible for the hypotonicity of amphibian urine and the absence of chlorid from it occur in the distal and not in the proximal tubule. The number and consistency of the results and the fact that they have been obtained with frogs as well as with Necturi leave little room for doubt as to the essential correctness of this statement.

It seems necessary to call attention to the difference between this conclusion and that reached by White and Schmitt[8] from observations made in 1926. By intracapsular injection they filled the lumen of a tubule of Necturus with a suspension of dog's red blood corpuscles stained with methylene blue. The blue stain could be seen in the tubule but no corpuscles could be discerned in it. They expressed the belief that the cells were "almost instantaneously" laked because of reabsorption of chlorid from the

injected fluid and that this must have occurred in the proximal tubule. We are sure that these observations were faulty* and regard it as regrettable that they have been accepted without confirmation by other experimenters.

Perhaps attention should be called also to an apparent inconsistency between our determinations of the total molecular concentration and chlorid concentration in fluid from the proximal tubule. The chlorid concentration seems to be slightly greater, the total concentration slightly less than those of plasma. The inconsistency lies in the fact that chlorid is the predominant factor in the total concentration. At present we can offer no other explanation for this than minor technical imperfections.

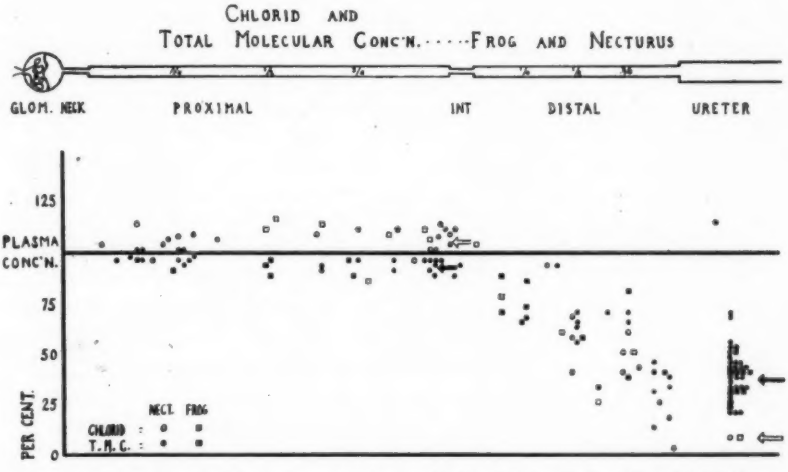

FIG. 2.—Total molecular concentration and chlorid concentration of fluid from the renal tubule. Distances along the abscissa indicate sites of collection. The results are shown as percentage differences from blood plasma. Arrows represent averages.

3. *The Reaction of Tubule Fluid.* Figure 3 shows the results of experiments by Drs. Montgomery and Pierce in which the pH of tubular fluid was determined by means of a microquinhydrone electrode.[36] It is clear that no significant change in reaction of the fluid occurs during passage through the proximal tubule; acidification, presumed to be due to reabsorption of bicarbonate, takes place exclusively in the distal tubule. This confirms a less precise observation made several years ago in which a phenol red solution introduced into a frog's tubule, was seen to change in color from red to yellow only after it had passed into the distal third of the entire tubule.

* Since this was written we have made careful repetitions of the experiments by White and Schmitt. The observations, which will be published elsewhere in detail, completely fail to agree with theirs.

4. *Glucose.* Figure 4 shows the concentrations of reducing substances in fluid taken from various levels of the tubule. Glomerular fluid contains glucose in the same concentration as plasma. No

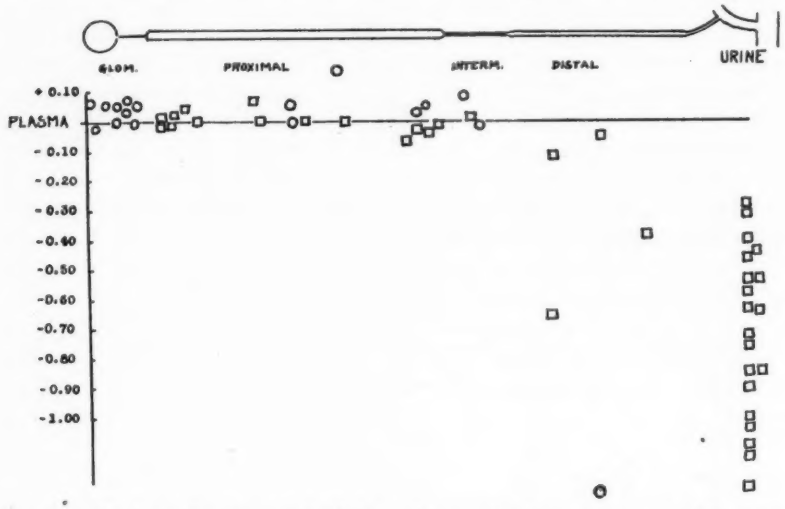

FIG. 3.—pH determinations of fluid from the renal tubule, shown as differences from those of plasma.

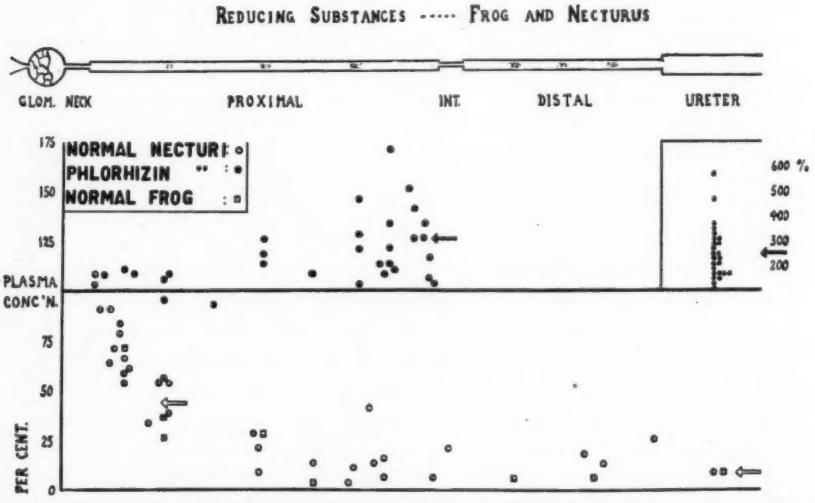

FIG. 4.—Reducing substances in fluid from the renal tubules shown as percentage differences from plasma. Open circles, normal Necturi; open squares, normal frogs; black circles, phlorhizinized Necturi. Arrows represent averages.

change occurs in passing through the neck of the tubule; the concentration diminishes rapidly as flow through the proximal tubule proceeds. When half of its length has been traversed the concen-

tration may be as low as it is in ureteral urine. The capacity of mediating the selective reabsorption of glucose is not however limited to the proximal half of the proximal tubule; for when Ringer's solution containing glucose is slowly perfused through the distal half of the proximal, the sugar disappears from it. When, however, a glucose solution is perfused through the distal tubule its concentration remains the same or increases. The sole site of selective glucose reabsorption, therefore, is the proximal tubule.

In Figure 4 is also shown a series of results which were obtained by analyzing tubule fluid from animals poisoned with phlorhizin. Since it is known that phlorhizin does not affect the glomerular filtration of glucose,[17] the meaning of these results is unmistakable. The action of phlorhizin on the kidney which results in glycosuria consists in abolition of the capacity of the cells of the proximal convoluted tubule to effect the selective reabsorption of glucose. This statement which agrees with current belief is based upon evidence more direct than that previously available.

The further question arose whether during the action of phlorhizin glucose, having reached a concentration in the tubule higher than that in the blood, can diffuse from the tubule into the blood. Does phlorhizin prevent passive diffusion as well as active reabsorption of glucose from the tubule? The question is important, for if it does, then the assumption, made by some workers in this field, that in phlorhizin poisoning *all* of the glucose contained in the glomerular filtrate leaves the kidney through the ureter is justified; and in that event the plasma clearance of glucose can be rightly accepted as a measure of the volume of glomerular filtration.

An answer to this question was obtained by perfusing, through the lumen of a proximal tubule of Necturus, Ringer's solution containing glucose in higher concentration than that in the blood plasma. The concentration in the recovered fluid was from 15 to 40% less than in the original fluid. Phlorhizin, therefore, does not prevent the escape of glucose from the renal tubule by diffusion.

A related question was studied, which concerns the behavior of xylose in the tubule. It was discovered by Jolliffe, Shannon and Smith[35] that the plasma clearance of xylose in the normal dog is the same as the glucose clearance in the dog poisoned by phlorhizin; and xylose clearance has come to be adopted by some investigators as a measure of glomerular filtration in normal animals. But when xylose solutions were perfused through the proximal tubules of frogs and Necturi the xylose concentrations decreased by 13 to 73%. Since these results cannot be explained by entrance of water into the tubule, we have confidence in saying that in a phlorhizinized tubule of Necturus, when the glucose concentration of the fluid passing through it reaches a certain excess over that of the blood, glucose diffuses back into the blood; and that in normal amphibia, xylose is capable of escaping from the tubule through

its wall. These conclusions are in harmony with those drawn from the study of the excretion of inulin by the dog.

The results obtained in the study of the change in the concentration of glucose which proceeds in the proximal tubules of phlorhizinized animals give strong evidence that the proximal tubule is the site of some of the water reabsorption. On the average, glucose is 26% more concentrated in the fluid which leaves the proximal tubule than in that which enters it. We know of no evidence which shows that the phlorhizinized tubule secretes glucose; much that it does not. Relying on this, we conclude that the increase in glucose concentration in the proximal tubule fluid is the result of an active reabsorption of water which amounts on the average to at least 20% of the volume of the glomerular filtrate.

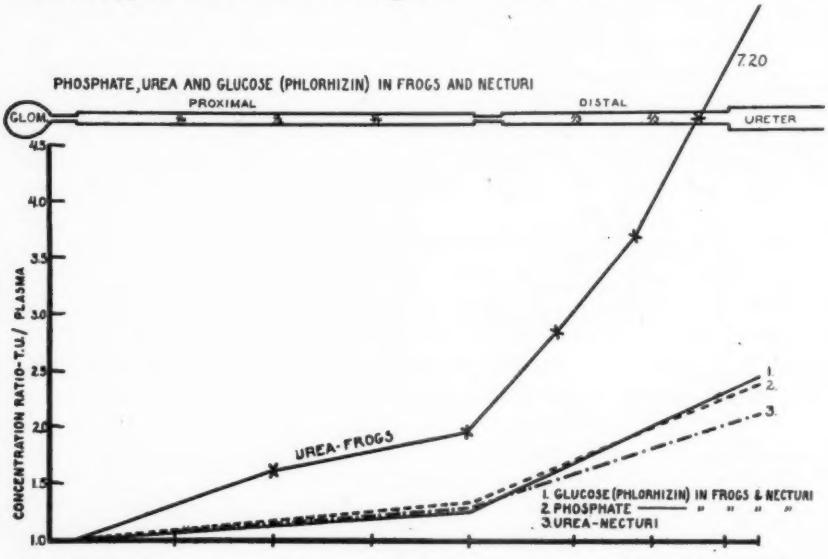

FIG. 5.—Average curves of analyses of tubule fluid for glucose in phlorhizin poisoning and urea and inorganic phosphates in normal animals.

Inorganic Phosphate, Urea, Uric Acid, Creatinin. Thus far we have discussed the functions of the tubule only in relation to substances which are reabsorbed in their passage through it: water, chlorid, bicarbonate, glucose. Something must now be said concerning the behavior of substances which are excreted in the urine in higher concentration than that in which they exist in plasma and in the glomerular filtrate. In this category we have studied inorganic phosphate, urea, uric acid and creatinin.

Figure 5 contains curves, each the composite of many experiments, which show the average changes in concentration which phosphate and urea undergo in their passage through the tubule.

Included also is the average curve which represents the increase in concentration which glucose undergoes in the phlorhizinized tubule. If, as we believe, this is the result of reabsorption of water it follows that similar change in concentration of another substance is similarly explainable.

Inorganic phosphate in both frogs and Necturi and urea in Necturi undergo, on the average, degrees of concentration so similar to that of glucose in phlorhizin poisoning that one explanation is adequate for all, namely, reabsorption of water. We see no necessity for assuming that in these experiments active secretion of phosphates was a factor. The case is different, however, with urea in the frog's tubule. It is possible, though not necessarily certain, that the concentration at the end of the proximal tubule (double that of glomerular fluid) cannot be explained by water reabsorption but that some urea was secreted. The most striking feature of the urea curve, however, is the steep rise in concentration which takes place in the distal tubule. The average concentration ratio attained (7.2) is derived from figures which go as high as 20. If secretion of urea is a factor in the production of these high concentrations the suspicion is aroused that the distal tubule is its chief site. What is urgently needed in further experiments of this sort is some more conclusive method of measuring the absorption of water from the tubule.

In studying the changes in concentration which uric acid and creatinin of the glomerular filtrate undergo in passing through the tubule, it was necessary to inject both substances before beginning an experiment because of the small amounts normally present in the blood. In frogs the changes in uric acid were similar to, though not so pronounced as those of urea; in Necturi its concentration may increase slightly or may decrease during passage through the tubule. The results give no reason to think that it is secreted by the tubule of Necturus; we are uncertain about the frog's tubule.

Creatinin in the frog's tubule behaved like uric acid in Necturus; there was no increase in concentration sufficient to suggest secretion; often there was a decrease. In a few experiments with Necturus, however, creatinin became more concentrated in the proximal tubule than any other substance yet studied by these methods. It may well be that this is indicative of a secretory process for creatinin operative in the proximal tubule of Necturus, not in that of the frog.

The most striking outcome of these experiments, aside from the scanty evidence they afford of the existence of secretory processes in the epithelium of the proximal tubule, is the demonstration of radical differences in the behavior of urea, uric acid and creatinin in the tubules of the two species studied. Results obtained with one are definitely not transferable to the other. Obviously it would

be even more hazardous to draw conclusions concerning secretion by the mammalian tubule from these results.

We have hope and some expectation that the methods which have been developed in these studies will be found applicable to the mammalian kidney. It seems not unreasonable to anticipate that when that objective is attained it will be found that the reabsorptive processes, so conspicuously apparent and definitely localizable in the amphibian tubule and so fundamentally important for survival, will be found in the analogous sections of the tubule of the mammal.

REFERENCES.

1. Richards, A. N.: Harvey Lectures, **16**, 163, 1920–1921; Am. J. Med. Sci., **163**, 1, 1922.
2. Nussbaum, M.: Pflüger's Arch. f. d. ges. Physiol., **16**, 139, 1878; **17**, 580, 1878.
3. Bainbridge, F. A., and Beddard, A. P.: Biochem. J., **1**, 255, 1906.
4. Cullis, W. E.: J. Physiol., **34**, 250, 1906.
5. Hill, L., and McQueen, J.: Brit. J. Exp. Path., **2**, 205, 1921.
6. Richards, A. N., and Schmidt, C. F.: Am. J. Physiol., **71**, 178, 1924.
7. Wearn, J. T., and Richards, A. N.: Ibid., p. 209.
8. White, H. L., and Schmitt, F. O.: Science, **62**, 334, 1925; Am. J. Physiol., **76**, 483, 1926.
9. Walker, A. M.: J. Biol. Chem., **87**, 499, 1930.
10. White, H. L.: Am. J. Physiol., **85**, 191, 1928.
11. Bayliss, L. E., and Walker, A. M.: J. Biol. Chem., **87**, 523, 1930.
12. Westfall, B. B., Findley, T. E., and Richards, A. N.: Ibid., **107**, 661, 1934.
13. Wearn, J. T., and Richards, A. N.: Ibid., **66**, 247, 1925.
14. Freeman, B., Livingston A. E., and Richards, A. N.: Ibid., **87**, 467, 1930.
15. Ekehorn, G.: On the Principles of Renal Function, Acta med. Scandin., Suppl., **36**, 317, 1931.
16. Walker, A. M.: J. Biol. Chem., **101**, 239, 1933.
17. Walker, A. M., and Reisinger, J. A.: Ibid., p. 223.
18. Bordley, J., and Richards, A. N.: Ibid., p. 193.
19. Bordley, J., Hendrix, J. P., and Richards, A. N.: Ibid., p. 255.
20. Richards, A. N., and Walker, A. M.: Ibid., **87**, 479, 1930.
21. Montgomery, H.: Ibid., **110**, 749, 1935.
22. Walker, A. M., and Elsom, K. A.: Ibid., **91**, 593, 1931.
23. Hayman, J. M.: Am. J. Physiol., **79**, 389, 1927.
24. White, H. L.: Ibid., **90**, 689, 1929.
25. Bensley, R. R., and Steen, W. B.: Am. J. Anat., **41**, 75, 1928. Holton, S. G., and Bensley, R. R.: Ibid., **47**, 241, 1931.
26. Drew, H. D. K., and Haworth, W. N.: J. Chem. Soc., p. 2690, 1928. Haworth, W. N., Hirst, E. L., and Percival, E. G. V.: Ibid., p. 2384, 1932.
27. Irvine, J. C., and Montgomery, T. N.: J. Am. Chem. Soc., **55**, 1988, 1933.
28. Greenberg, D. M., and Gunther, L.: J. Biol. Chem., **85**, 491, 1930.
29. Oliver, J., and Shevky, E.: J. Exp. Med., **50**, 15, 1929.
30. Marshall, E. K., Jr., and Crane, M. M.: Am. J. Physiol., **70**, 465, 1924. Crane, M. M.: Ibid., **81**, 232, 1927. Marshall, E. K., Jr.: J. Cell. and Comp. Physiol., **2**, 349, 1932–33; Physiol. Rev., **14**, 149, 1934.
31. Marshall, E. K., Jr., and Vickers, J. L.: Bull. Johns Hopkins Hosp., **34**, 1, 1923. Marshall: Am. J. Physiol., **99**, 77, 1931.
32. Richards, A. N., Westfall, B. B., and Bott, P. A.: Proc. Soc. Exp. Med. and Biol., **32**, 73, 1934–35.
33. Kunkel, P. A., Jr.: Bull. Johns Hopkins Hosp., **47**, 285, 1930.
34. Rehberg, P. B.: Biochem. J., **20**, 447, 1926.
35. Jolliffe, N., Shannon, J. A., and Smith, H. W.: Am. J. Physiol., **100**, 301, 1932.
36. Pierce, J. A., and Montgomery, H.: J. Biol. Chem., **110**, 763, 1935.

(Titles have been omitted for the sake of brevity.)

THE URINARY CONCENTRATION IN DIABETES INSIPIDUS.

A Comparison of the Effects of Several Drugs.

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Many drugs have been studied and recommended in the therapy of diabetes insipidus, but, at present, derivatives of the posterior lobe of the pituitary gland have largely replaced all others. The work of Scherf,[1] however, has recently aroused interest in amidopyrin, and Kahn[2] has reported a case successfully treated by this substance. F. M. Smith[3] has called attention to the economic aspect of treatment and has shown that the insufflation of powdered posterior pituitary substance is just as efficient and far cheaper than the usual extracts given subcutaneously. Smith's observations have been confirmed by Canelo and Lisser.[10]

It seemed desirable, therefore, to attempt to compare the effect of some of these drugs on the urinary concentration. Two cases of diabetes insipidus fortunately became available for this work.

Methods. During the periods of study the patients were confined to bed and the utmost precautions were taken not to suggest the outcome of tests or therapy. When a drug was to be tried, a control period was used during which a suitable placebo was administered. They were invariably able to distinguish the potent drugs by the effect on thirst and diuresis.

A standard test was devised to study the effect of various drugs on urinary concentration. It seemed desirable to eliminate the factor of thirst. A typical test period ran for 48 hours, starting at 6 A.M. At that time, and at 2-hour intervals, the patient drank 500 cc. of water and emptied the bladder. She was awakened at night for this purpose. The placebo, in the form of tablets, capsules or hypodermic injections of distilled water, was given at 10 A.M. of the first day and the trial drug was given at the same time the next day. During the 2 days, 6 identical meals were served to control the water and chlorid intake from that source. The 2-hour urine specimens were examined for color, the volume was measured, and the specific gravity determined with the urinometer.

The specific gravity of the urine was taken as an indication of the concentration of dissolved solids in the urine.[4,5] While diminution in volume output during the 2-hour periods was noted, and corresponded fairly well with increased specific gravity, yet volume output as measured in these tests is subject to variation from other factors, such as the voluntary control of the bladder

and variations in water balance which may have no apparent relation to the problem at hand. It would therefore appear that increase in the specific gravity of the urine seems to be a more accurate index of the potency of antidiuretic drugs in diabetes insipidus.

Case Reports. CASE 1.—L. O., housewife, aged 42, was under observation from July, 1933, to March, 1934. She had apparently been in good health until October, 1921, when polydipsia and polyuria first occurred. Several months later she was studied in a private hospital, where her urinary output averaged 16 quarts (15 liters) in 24 hours. The diagnosis of diabetes insipidus was made then. Since that time the diuresis had been continuous but the daily output had gradually diminished. Among her numerous complaints were pain in the hips, headache, emotional instability, transient paralyses, and "fainting spells." She had been a semi-invalid for the last year because of fear of falling. The previous medical history was not significant except that she had given birth to a child precipitately 9 months before the onset of the diuresis.

Physical examination revealed no abnormalities except a moderately enlarged heart. She weighed 145 pounds and was 61 inches tall. Repeated neurologic examinations were negative. The neurologists were forced to explain her many complaints on the basis of hysteria. The ocular fundi were normal and the visual fields were not impaired. No remnants of Rathke's pouch were found. Teleoroentgenogram gave a Danzer ratio of 0.57. Electrocardiogram showed slight left axis deviation. The basal metabolic rate was −6%. Blood counts were normal. Blood Kahn and Wassermann tests were negative. Blood urea, uric acid, creatinin, calcium and phosphorus determinations were repeatedly normal.

When she was allowed to drink freely, the average fluid intake in 24 hours, excluding water in the food, was 6430 cc. and the urinary output was 5672 cc. The daily (6 A.M. to 6 P.M.) intake slightly exceeded the night intake, whereas the nocturnal output was usually greater than the diurnal. The urine was examined frequently but no casts or cellular elements were ever found in excess. Glucose and albumin were never noted. The specific gravity never exceeded 1.004 except when specific medication was given.

Results. The drugs studied were amidopyrin (Pyramidon), acetyl salicylic acid (aspirin), antipyrin, acetphenetidin (phenacetin), vasopressor fraction of posterior pituitary gland (pitressin—Parke, Davis & Co.), histamin, morphin sulphate, sodium bromid and powdered posterior pituitary substance (Eli Lilly & Co.).

During the control periods of the tests the specific gravity of the urine never exceeded 1.004, while the 2-hourly fluid output varied between 240 cc. and 870 cc. with an average of around 500 cc. Some of the variation between the volumes of different specimens may be accounted for by the fact that the capacity of the bladder was found to be 1400 cc. and it may not have been possible to empty it completely each time. There was no constant change in urinary volume or specific gravity which could be ascribed to the ingestion of food.

Posterior Pituitary Gland. Two substances were studied: The vasopressor fraction known as "pitressin" (Parke, Davis & Co.), and a powdered preparation of the posterior lobe (Eli Lilly & Co.),

TABLE 1 (CASE 1).—PITRESSIN.

Date, 1933.	Time.	Volume intake, cc.	Urine.		All meals identical in composition.
			Volume, cc.	Specific gravity.	
December 11	6 A.M.— 8 A.M.	500	660	1.001	7 A.M. meal.
	8 " —10 "	"	580	1.002	
	10 " —12 M.	"	560	1.003	10 A.M. *sterile water* (hypo).
	12 M. — 2 P.M.	"	420	1.003	12 M. meal.
	2 P.M.— 4 "	"	540	1.004	
	4 " — 6 "	"	440	1.004	5:30 P.M. meal.
	6 " — 8 "	"	520	1.004	
	8 " —10 "	"	820	1.003	
	10 " —12 "	"	340	1.003	
December 12	12 " — 2 A.M.	"	780	1.003	
	2 A.M.— 4 "	"	410	1.003	
	4 " — 6 "	"	640	1.003	
	6 " — 8 "	"	330	1.003	7 A.M. meal.
	8 " —10 "	"	810	1.003	
		Total 7000	Total 7850		
	10 A.M.—12 M.	500	240	1.006	10 A.M. 1 cc. *pitressin* (hypo).
	12 M. — 2 P.M.	"	100	1.015	12 M. meal.
	2 P.M.— 4 "	"	100	1.015	
	4 " — 6 "	"	110	1.010	5:30 P.M. meal.
	6 " — 8 "	"	150	1.012	
	8 " —10 "	"	270	1.006	
	10 " —12 "	"	300	1.006	
December 13	12 " — 2 A.M.	"	220	1.005	
	2 A.M.— 4 "	"	490	1.004	
	4 " — 6 "	"	430	1.003	
		Total 5000	Total 2410		
	6 A.M.— 8 A.M.	400	580	1.004	7 A.M. meal.
	8 " —10 "	200	540	1.003	
	10 " —12 M.	400	670	1.003	
	12 M. — 2 P.M.	200	490	1.000	12 M. meal.
	2 P.M.— 4 "	400	550	1.003	
	4 " — 6 "	400	430	1.004	5:30 P.M. meal.
	6 " — 8 "	400	450	1.004	
	8 " —10 "	200	450	1.000	
	10 " —12 "	200	410	1.002	
December 14	12 " — 2 A.M.	200	360	1.004	
	2 A.M.— 4 "	200	270	1.002	
	4 " — 6 "	200	610	1.003	
		Total 3400	Total 5810		
		Grand total 15,400	Grand total 16,070		

representing 5 times the weight of the wet gland. Attention has been called to the latter substance by F. M. Smith.[3]

Table 1 shows the effect of 1 cc. pitressin hypodermically upon the volume output and the specific gravity of the urine. During the first 2-hour period the volume was 240 cc. and specific gravity 1.006. In the next period the volume was reduced to 100 cc. and the specific gravity was 1.015. The effect of the dose is seen to last from 10 A.M. to 2 A.M. (16 hours) with the maximum effect from 2 to 6 hours after administration. During the time when this drug was acting, the patient was drinking 500 cc. of water every 2 hours and urinating only 20 to 30% of it. Twenty hours after injection the patient had drunk 5000 cc. of water and excreted only 2410 cc., withholding 2590 cc. In a supplementary 24-hour period she was allowed to drink as much as desired and her output finally exceeded her intake. This supplementary period was not repeated in subsequent tests.

TABLE 2 (CASE 1).—POWDERED POSTERIOR PITUITARY SUBSTANCE.

Date, 1934.	Time.	Volume intake, cc.	Urine.		All meals identical in composition.
			Volume, cc.	Specific gravity.	
March 13	6 A.M.— 8 A.M.	500	330	1.002	7 A.M. meal.
	8 " —10 "	"	50	1.028	8 A.M. 0.05 gm. *powdered posterior pituitary* in nose.
	10 " —12 M.	"	120	1.012	
	12 M. — 2 P.M.	"	100	1.010	12 M. 0.05 gm. *powdered posterior pituitary* in nose. 12 M. meal.
	2 P.M.— 4 "	"	60	1.028	
	4 " — 6 "	"	110	1.020	4 P.M. 0.05 gm. *powdered posterior pituitary* in nose. 5:30 P.M. meal.
	6 " — 8 "	"	120	1.016	
	8 " —10 "	"	400	1.006	
	10 " —12 "	"	610	1.004	
March 14	12 " — 2 A.M.	"	530	1.003	
	2 A.M.— 4 "	"	800	1.002	
	4 " — 6 "	"	850	1.001	
March 15	6 " — 8 "	"	500	1.001	7 A.M. meal.
	8 " —10 "	"	470	1.003	8 A.M. 0.05 gm. *powdered posterior pituitary* under tongue.
	10 " —12 M.	"	640	1.002	
	12 M. — 2 P.M.	"	430	1.003	12 M. meal.
	2 P.M.— 4 "	"	830	1.002	
	4 " — 6 "	"	470	1.003	4 P.M. 0.1 gm. *powdered posterior pituitary* by mouth. 5:30 P.M. meal.
	6 " — 8 "	"	470	1.000	
	8 " —10 "	"	710	1.001	
	10 " —12 "	"	660	1.001	
March 16	12 " — 2 A.M.	"	670	1.002	
	2 A.M.— 4 "	"	540	1.001	
	4 " — 6 "	"	660	1.001	

Table 2 shows the results of the administration of powdered posterior pituitary substance intranasally, under the tongue, and orally. The 2-hour output of urine was reduced to 50 or 60 cc. and the specific gravity was raised to 1.028 on 2 occasions by the administration of 50 mg. of the powder in the nose. Fifty milli-

grams of the powder had no effect under the tongue and 100 mg. by mouth 4 hours after a meal were likewise ineffectual.

For nasal administration single doses of the powder were weighed out into papers and the dose taken up in a dry medicine dropper and insufflated well into the nares. The patient was sent home at one time with instructions to take 50 mg. of the powdered substance intranasally 3 times daily. The drug was very effective but the patient complained that the nasal mucosa became painful and that the powder tended to form crusts in the nares.

Each of the following drugs was administered in the course of a separate 48-hour test period, exactly duplicating the first 48 hours outlined for pitressin.

TABLE 3 (CASE 1).—AMIDOPYRIN.

Date. 1933.	Time.	Volume intake, cc.	Urine.		All meals identical in composition.
			Volume, cc.	Specific gravity.	
November 1	6 A.M.— 8 A.M.	500	420	1.001	7 A.M. meal.
	8 " —10 "	"	480	1.002	
	10 " —12 M.	"	670	1.002	10 A.M. *placebo tablets.*
	12 M. — 2 P.M.	"	350	1.004	12 M. meal.
	2 P.M.— 4 "	"	410	1.003	
	4 " — 6 "	"	420	1.004	5:30 P.M. meal.
	6 " — 8 "	"	410	1.004	
	8 " —10 "	"	510	1.001	
	10 " —12 "	"	430	1.003	
November 2	12 " — 2 A.M.	"	290	1.003	
	2 A.M.— 4 "	"	610	1.003	
	4 " — 6 "	"	590	1.002	
	6 " — 8 "	"	360	1.000	7 A.M. meal.
	8 " —10 "	"	640	1.003	
	10 " —12 M.	"	130	1.007	10 A.M. 2 gm. *amidopyrin* by mouth. Urine pink.
	12 M. — 2 P.M.	"	80	1.011	12 M. meal. Urine orange.
	2 P.M.— 4 "	"	210	1.005	Urine pink.
	4 " — 6 "	"	280	1.005	5:30 P.M. meal. Urine pink.
	6 " — 8 "	"	430	1.004	Urine pink.
	8 " —10 "	"	190	1.003	Urine pink.
	10 " —12 "	"	70	1.004	Urine pink.
November 3	12 " — 2 A.M.	"	350	1.004	Urine reddish.
	2 A.M.— 4 "	"	280	1.001	Urine pink.
	4 " — 6 "	"	600	1.003	Urine pink.

Amidopyrin. The use of this drug was suggested by Scherf.[1] Table 3 shows the effect of the ingestion of 2 gm. In the second 2-hour period the urinary output was only 80 cc. and the specific gravity 1.011. The effect lasted about 8 hours in all, but the maximum was from 2 to 4 hours. The urine was colored orange by the drug and some trace of color was seen as long as 18 hours after administration of the single dose.

During several weeks in the hospital the diuresis was controlled to the patient's satisfaction, at least, by the oral administration of

1 gm. of amidopyrin before retiring. Whereas she usually awoke 5 or 6 times to void, she was enabled to sleep through the night, arising only once or not at all. In comparing day and night specimens it was rather puzzling to note that the nocturnal output was not much decreased in spite of the patient's observations. The urologist found that the capacity of her bladder was 1400 cc., and while the specific gravity of the night urine was somewhat higher than the diurnal, yet it is possible that the drug also tended to diminish the irritability of the bladder. The patient also reported that her thirst was much relieved. In spite of our objective evidence that the intranasal pituitary powder was much more effective, she voluntarily reverted to the use of amidopyrin while at home because of the local irritation caused by the powder.

Neutropenia did not develop after the administration of the drug for several months.

Sodium Bromid. Two grams sodium bromid by mouth produced no effect on the urinary concentration or volume output in a standard 48-hour test.

Morphin Sulphate. One one-hundredth gram morphin sulphate subcutaneously had no effect as judged by a 48-hour test period.

Histamin. This drug was tried because Gibson and Martin[6] reported that it was effective in 1 case. In our case 0.003 gm. was given subcutaneously and, although the typical headache and peripheral vasodilatation were obtained, there was no effect on the specific gravity of the urine. It is possible, however, that in collecting 2-hour specimens of urine a transient effect may have been masked.

Acetphenetidin. No effect was noted in a standardized test after the ingestion of 2 gm. of the drug. The urine was colored brown for 4 hours after ingestion.

Acetyl Salicylic Acid. The administration of 2 gm. by mouth caused an increase in the urinary specific gravity to 1.006 in the period 2 to 4 hours after ingestion. The 2-hour output was 290 cc.

Antipyrin. Two grams of the drug by mouth caused the 2-hour urinary outputs to be reduced to 210 cc. and 150 cc. for the 2 periods following administration. The specific gravities for the 2 periods were 1.006 and 1.009 respectively. Eichhorst,[7] in 1888, reported that this drug effectively controlled the diuresis.

CASE 2.—A. D., housewife, aged 56, was studied in the University Hospital from January 5 to February 21, 1935. She had had polydipsia and polyuria for about 1 year, the symptoms increasing in severity 5 months before admission. She had lost 20 pounds in weight associated with anorexia. For 6 months she had noted a mass in the lower abdomen which had slowly increased in size.

She was apparently quite weak and undernourished. The skin was dry and rough. The abdomen was distorted by a globular tumor arising from the pelvis and extending nearly to the umbilicus. The cervix uteri appeared normal and the tumor appeared to be associated with the fundus uteri.

Blood counts showed a slight secondary anemia. Basal metabolic rate was +9%. The visual fields were not impaired. Roentgenologic studies of the skull, chest and gastro-intestinal tract revealed no abnormalities.

During a 5-day period she drank fluids *ad libitum* and the average 24-hour urinary volume was 6120 cc. The maximum specific gravity of these specimens was 1.002. A series of concentration tests previously described in Case 1 was then employed. She was then transferred to the Department of Gynecology, where surgical exploration was performed. The tumor mass was found to be an adenocarcinoma of both ovaries and endometrium (Krukenberg type). There was an area of induration in the stomach which was thought to be a possible primary focus. There was no evidence of other metastases and no involvement of the nerve supply to the kidneys.

For 10 days postoperation the 24-hour urinary output averaged 1200 cc., although fluids were not restricted. This was thought to be due to the lumbar puncture by which anesthesia had been obtained. After this period, diuresis was controlled by 50 mg. powdered posterior pituitary substance intranasally at 7 A.M. and 7 P.M.

She received deep Roentgen ray therapy and was sent home, where she died March 2, 1935. No autopsy was performed.

Results. The effect of 4 drugs on the urinary concentration was studied by means of the standardized test devised.

Pitressin. One cubic centimeter of pitressin (hypo) only concentrated the urine to a specific gravity of 1.008. The minimum 2-hourly output during this test was 90 cc. Details are set forth in Table 4.

TABLE 4 (CASE 2).—PITRESSIN.

Date, 1935.	Time.	Volume intake, cc.	Urine.		All meals identical in composition.
			Volume, cc.	Specific gravity.	
January 13	6 A.M.— 8 A.M.	500	640	1.000	7 A.M. meal.
	8 " —10 "	"	720	1.001	
	10 " —12 M.	"	680	1.003	10 A.M. *sterile water* (hypo).
	12 M. — 2 P.M.	"	660	1.003	12 M. meal.
	2 P.M.— 4 "	"	790	1.001	
	4 " — 6 "	"	430	1.003	5:30 P.M. meal.
	6 " — 8 "	"	660	1.002	
	8 " —10 "	"	660	1.001	
	10 " —12 "	"	470	1.004	
January 14	12 " — 2 A.M.	"	610	1.003	
	2 A.M.— 4 "	"	390	1.001	
	4 " — 6 "	"	560	1.003	
	6 " — 8 "	"	460	1.003	7 A.M. meal.
	8 " —10 "	"	440	1.003	
	10 " —12 M.	"	90	1.005	10 A.M. 1 cc. *pitressin* (hypo).
	12 M. — 2 P.M.	"	130	1.008	12 M. meal.
	2 P.M.— 4 "	"	190	1.008	
	4 " — 6 "	"	150	1.003	5:30 P.M. meal.
	6 " — 8 "	"	300	1.004	
	8 " —10 "	"	310	1.004	
	10 " —12 "	"	170	1.005	
January 15	12 " — 2 A.M.	"	150	1.006	
	2 A.M.— 4 "	"	110	1.003	
	4 " — 6 "	"	260	1.000	

Powdered Posterior Pituitary Substance (Table 5). A single 50 mg. dose in the nose induced a maximum specific gravity of the urine of 1.017. The minimum volume output for 2 hours was 18 cc.

TABLE 5 (CASE 2).—POWDERED POSTERIOR PITUITARY SUBSTANCE.

Date, 1935.	Time.	Volume intake, cc.	Urine.		All meals identical in composition.
			Volume, cc.	Specific gravity.	
January 16	6 A.M.— 8 A.M.	500	630	1.002	7 A.M. meal.
	8 " —10 "	"	570	1.003	
	10 " —12 M.	"	180	1.009	10 A.M. 0.05 gm. *powdered posterior pituitary substance* nasally.
	12 M. — 2 P.M.	"	18	1.014	12 M. meal.
	2 P.M.— 4 "	"	45	1.016	
	4 " — 6 "	"	80	1.017	5:30 P.M. meal.
	6 " — 8 "	"	65	1.017	
	8 " —10 "	"	430	1.004	
	10 " —12 "	"	420	1.004	
January 17	12 " — 2 A.M.	"	300	1.002	
	2 A.M.— 4 "	"	340	1.003	
	4 " — 6 "	"	430	1.001	

TABLE 6 (CASE 2).—AMIDOPYRIN.

Date, 1935.	Time.	Volume intake, cc.	Urine.		All meals identical in composition.
			Volume, cc.	Specific gravity.	
January 18	6 A.M.— 8 A.M.	500	610	1.001	7 A.M. meal.
	8 " —10 "	"	660	1.001	
	10 " —12 M.	"	320	1.003	10 A.M. 2 gm. *amidopyrin* by mouth. Urine pink.
	12 M. — 2 P.M.	"	190	1.005	12 M. meal. Urine pink.
	2 P.M.— 4 "	"	22	1.005	Urine pink.
	4 " — 6 "	"	100	1.007	5:30 P.M. meal. Urine orange.
	6 " — 8 "	"	90	1.010	Urine red.
	8 " —10 "	"	100	1.007	Urine red.
	10 " —12 "	"	80	1.009	Urine red.
January 19	12 " — 2 A.M.	"	40	1.011	Urine orange.
	2 A.M.— 4 "	"	70	1.012	Urine pink.
	4 " — 6 "	"	170	1.007	Urine pink.

Amidopyrin (Table 6). Two grams by mouth caused a maximum specific gravity of 1.012 and a minimum 2-hour output of 22 cc. For some undetermined cause the action of this drug was much prolonged in Case 2.

Obstetrical Pituitrin (Table 7). One cubic centimeter of this drug hypodermically produced a slight concentration in the urine (specific gravity 1.005).

TABLE 7 (CASE 2).—PITUITRIN.

Date, 1935.	Time.	Volume intake, cc.	Urine. Volume, cc.	Urine. Specific gravity.	All meals identical in composition.
January 20	6 A.M.— 8 A.M.	500	690	1.000	7 A.M. meal.
	8 " —10 "	"	720	1.002	
	10 " —12 M.	"	200	1.005	10 A.M. 1 cc. *obstetrical pituitrin* (hypo).
	12 M. — 2 P.M.	"	270	1.005	12 M. meal.
	2 P.M.— 4 "	"	360	1.003	
	4 " — 6 "	"	430	1.004	5:30 P.M. meal.
	6 " — 8 "	"	470	1.003	
	8 " —10 "	"	460	1.003	
	10 " —12 "	"	320	1.003	
January 21	12 " — 2 A.M.	"	430	1.003	
	2 A.M.— 4 "	"	270	1.002	
	4 " — 6 "	"	260	1.003	

Summary. Two cases of diabetes insipidus of unknown etiology have been studied with reference to the effect of various drugs on the concentration of the urine.

A test has been devised which allows an evaluation and comparison of the effect of drugs on the urinary concentration. This test eliminates the factor of thirst from consideration.

If the maximum specific gravity of a 2-hour urine specimen obtained under conditions of the test be taken as an index of the effect of the drug in Case 1, the drugs can be ranged in the following order of potency:

	Specific gravity.
0.05 gm. powdered posterior pituitary substance (intranasally)	1.028
1 cc. pitressin (hypodermically)	1.015
2 gm. amidopyrin (orally)	1.011
2 gm. antipyrin (orally)	1.009
2 gm. acetyl salicylic acid (orally)	1.006
2 gm. acetphenetidin (orally)	No effect
2 gm. sodium bromid (orally)	No effect
0.003 gm. histamin (hypodermically)	No effect
0.01 gm. morphin sulphate (hypodermically)	No effect

In Case 2 a similar comparison can be made:

	Specific gravity.
0.05 gm. powdered posterior pituitary substance (intranasally)	1.017
2 gm. amidopyrin (orally)	1.012
1 cc. pitressin (hypodermically)	1.008
1 cc. obstetrical pituitrin (hypodermically)	1.005

These results supplement the studies of F. M. Smith[3] and Vidgoff[8] on the effects of the nasal insufflation of powdered posterior pituitary substance. In Smith's experiments the possibility of some effect of the drug on thirst was not eliminated. The tests confirm Eichhorst's

report[7] on the efficacy of antipyrin. The reports of Scherf[1] and Kahn[2] as to the value of amidopyrin are also confirmed. In view of the recent reports of the occurrence of agranulocytosis following aministration of admidopyrin,[9] this drug should be used with caution.

REFERENCES.

1. Scherf, D.: Pyramidon beim Diabetes Insipidus, Wien. Arch. f. inn. Med., **22**, 457, 1932.
2. Kahn, B. S.: The Use of Amidopyrine in a Case of Diabetes Insipidus, J. Am. Med. Assn., **100**, 1593, 1933.
3. Smith, F. M.: Diabetes Insipidus. Treatment by Intranasal Insufflation of Posterior Lobe Pituitary Powder, Ibid., **102**, 660, 1934.
4. Long, J. H.: On the Relation of the Specific Gravity of Urine to the Solids Present (second paper), J. Am. Chem. Soc., **25**, 871, 1903.
5. Lashmet, F. H., and Newburgh, L. H.: The Specific Gravity of the Urine as a Test of Kidney Function, J. Am. Med. Assn., **94**, 1883, 1930.
6. Gibson, R. B., and Martin, F. T.: Administration of a Pituitary Extract and Histamine in a Case of Diabetes Insipidus, Arch. Int. Med., **27**, 351, 1921.
7. Eichhorst, H.: Praktische Erfahrungen über die zuckerige und einfache Harnruhr, Cor.-Bl. f. schweiz. Ärtze, **18**, 393, 1888.
8. Vidgoff, B.: Posterior Pituitary Therapy in Diabetes Insipidus, Endocrinology, **16**, 289, 1932.
9. Madison, F. W., and Squier, T. L.: The Etiology of Primary Granulocytopenia (Agranulocytic Angina), J. Am. Med. Assn., **102**, 755, 1934.
10. Canelo, C. K., and Lisser, H.: A case of Diabetes Insipidus, California and West. Med. **42**, 178, 1935.

THE NATURE OF OSTEOGENESIS IMPERFECTA.*

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The purpose of this report is to present the results of an extensive clinical investigation of a typical case of *osteogenesis imperfecta.*

Armand[1] reported as early as 1716 a case of this disease. A thorough clinical and probably the first anatomic description was made by v. Lobstein[2] in 1833. The term "Lobstein's disease" is still encountered. He applied the name "idiopathic osteopsathyrosis." Henzschel[3] noted the blue scleræ in 1831. In 1848, the blue scleræ and multiple fractures were associated with this disease by Cornaz.[4]

The china or slate-blue scleræ are characteristic. Their color

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is due to partial visibility of the underlying choroid. The bone fragility is so increased that even slight trauma may produce fractures. Fractures occur from the intrauterine period to advanced age, are most common in infancy and early youth, and decrease at puberty. They occur almost exclusively in the shafts of the long bones and in the ribs. There is little or no associated pain, and the bones usually heal rapidly.

Deafness, associated with otosclerosis,[5] usually occurs in the second decade. It accompanies the blue scleræ and brittle bones in 40% of the cases.[5] Heredity was a factor in 28% of the cases collected by Fairbank.[6]

The pathologic findings are presented in the excellent monograph of Key.[7] Necropsy has revealed no major pathologic process save in the bones.[8] A decrease in osteoblasts and a defective production of osteoid tissue have been noted.[9,10]

The etiology is obscure. Some investigators suspect a faulty metabolism resulting from various endocrine disturbances. On the other hand, the endocrine glands have been found normal at necropsy by Kraus[11] and recently by Hennessy.[12] The calcium and phosphorus content of the affected bones are normal.[13,14] The serum calcium and phosphorus, as well as the calcium balance, remain within normal range, as revealed by the data we are about to report, and by Hunter's[15,16] and Klercker's[17] investigations. The thymus has been suspected. Gorter, quoted by Fairbank,[6] and Ryan[18] reported improvement subsequent to the administration of thymus. Metabolic studies, however, were not made.

Others consider a developmental anomaly of the mesoblast. Bauer[9] was one of the first to advocate this theory. He suggested a deficiency of all mesenchymal tissues and showed histologic abnormalities in bone, cartilage and tooth pulp. Key[7] regards the blue scleræ as evidence of an hereditary hypoplasia of the mesenchyma.

The disease may be due to a deficiency in phosphatase production. This "splitting enzyme" was described by Robison[19] in 1923. It is most plentiful in ossifying portions of normal bone. Robison's theory[19] has received support in the work of Kay,[20] who finds that the osteoblasts and hypertrophied cartilage cells secrete this enzyme. Crooks[21] reported in one instance an increased plasma phosphatase. The bone phosphatase in this disease has not been investigated, so far as we are aware.

Recently we have had the opportunity of investigating a typical instance of *osteogenesis imperfecta*. We were particularly interested in determining any relationship to hyperparathyroidism.

Case Report. B. N., No. 335288, a white male, aged 17, who was referred by Dr. P. L. Ring, Bellaire, Ohio, entered this hospital complaining of a multiplicity of painless fractures. His mother, who volunteered the following information, stated that although his delivery was normal, there

was at the time of birth, an abnormal contour of the right arm and left leg and slate-blue scleræ. About a week later it was learned that these deformities were due to fractures. Since that time he has sustained 48 fractures, all of which have involved the long bones and ribs, 40 occurring before the age of 11. Since then fractures have occurred with decreasing frequency. These fractures were accompanied by little or no pain, were easily reduced and readily healed by immobilization. There is no history of non-union and at no time was open reduction necessary. Occasionally there was mild discomfort but this disappeared in about 2 or 3 days. He became aware of his susceptibility to fractures and therefore avoided any trauma or sudden motion such as twisting or turning. Numerous Roentgenograms have been taken throughout his life. These revealed a "type of osteoporosis." His deciduous teeth were lost early. Many were lost while chewing food.

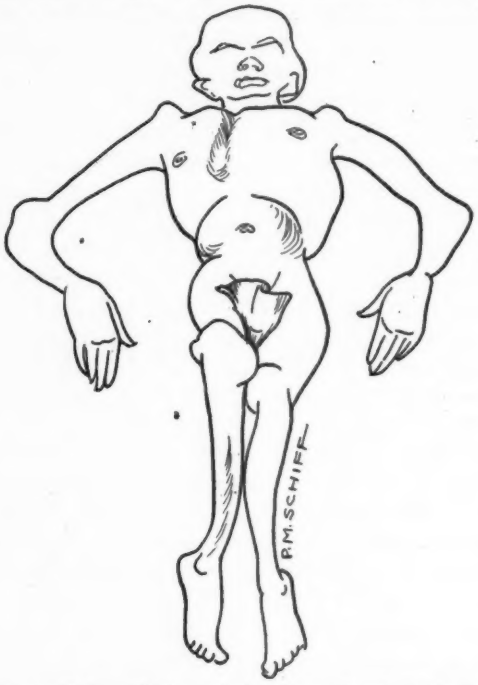

FIG. 1.—Osteogenesis imperfecta, anterior view, showing characteristic gross deformities, dwarfism and generalized muscular atrophy.

He has never been able to walk unaided. His chief means of locomotion is crawling, or walking with the aid of crutches. Because of his physical disability he was advised by his physicians to leave school after having passed the sixth grade. His appetite has always been good and there has been no diarrhea or constipation.

He has had the usual childhood diseases such as measles, mumps, scarlet fever, and chickenpox. His family history revealed that no other members were subject to such a multiplicity of fractures. However, two brothers had definite blue scleræ. Information obtained from his grandparents revealed that none of his remote relatives was known to be afflicted with this type of bone disease.

Physical examination revealed a poorly nourished, under-developed, dwarfed white male, 3½ feet in height, and weighing 44 pounds (Figs. 1 and 2).

Gross inspection of his body revealed what appeared to be generalized muscular atrophy. The head was characteristically shaped (Figs. 3 and 4). The zygomæ and mastoid processes were prominent, also the occiput, the latter increasing the antero-posterior diameter of the head. The hair was blond, and was normal in quantity and consistency. The eyebrows and eyelashes were black. These stood out in striking contrast to the color of the hair. Examination of the ears was negative. Hearing was normal to the whispered voice and tuning fork tests. The scleræ were of an intense slate-blue color. The pupils were round, equal and regular, and reacted to light and accommodation. Extraocular movements were normal. Eye ground examination was normal. The mouth was in poor condition. The mucous membrane was congested. The teeth were poorly developed, and many were carious and broken off at the gingival line. The tonsils were hypertrophied and cystic, but did not contain pus. The tongue was somewhat hypertrophied and furry. The breath was foul.

FIG. 2.—Osteogenesis imperfecta, posterior view, showing characteristic gross deformities, dwarfism and generalized muscular atrophy.

The chest (Figs. 1 and 2) was asymmetrical and deformed; the sternum prominent; the general contour that of a rachitic. The upper thoracic spine showed a scoliosis to the left. The antero-posterior diameter of the chest was increased. The ribs were not tender. No pulmonary or cardiac abnormality was noted. The abdomen was short (Fig. 1), but otherwise negative. A non-tender liver was palpated on inspiration at the right costal border. The pubic hair was sparse, the escutcheon masculine. The genitalia were normal in development. There was marked deformity of all extremities. Both upper extremities presented lateral bowing, most

pronounced in the radii and ulnæ. Both femora were abnormally short and greatly deformed. The legs presented obvious anterior bowing. The hands and feet, however, were normal. No exostoses were palpable on any of the extremities. Neurologic examination was normal throughout. Intelligence was normal.

Laboratory findings revealed negative Wassermann and Kahn tests. Repeated urine examinations failed to disclose any abnormalities. Phenol-

FIG. 3.—Osteogenesis imperfecta, showing the characteristically shaped head with bulging of the temporal regions.

FIG. 4.—Osteogenesis imperfecta, showing the characteristically shaped head with an unduly prominent occiput.

sulphonephthalein excretion, after intravenous injection, showed 80% elimination of the dye at the end of 1 hour, and 15% more at the end of the second. Repeated blood examinations revealed a red blood count of about 3,800,000; white blood count, 6300; hemoglobin (Newcomer), 10.9 gm. The differential count showed 80% neutrophils, 1% eosinophils, 15% lymphocytes, and 4% monocytes. The total plasma nitrogen was 900.6 mg.%; non-

FIG. 5.—The right femur, presenting the great disproportion between the size of the epiphysis and diaphysis.

FIG. 6.—The right femur. showing the usual type and site of fracture.

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FIG. 7

FIG. 8

FIG. 7.—A fracture of the upper end of the left humerus and lateral bowing in the region of the elbow.

Fig. 8.—The right femur in 1931, showing no sites of the numerous old fractures. Also showing "a foamy epiphysis," and mottling of the metaphysis. The diaphysis is particularly involved and presents a concentric type of atrophy.

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FIG. 9.—Marked anterior bowing of the leg bones independent of fractures.

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protein nitrogen 22.7 mg.%; blood urea was 18 mg.%; plasma protein was calculated as 5.5%. The basal metabolic rates, on two determinations, were +11 and +7, respectively.

Roentgenographic Study. A complete roentgenographic study of the skeleton of this patient was made. There were also available roentgenograms of the 15 treated fractures sustained since 1927, during a period of 7 years. These fractures had occurred with decreasing frequency. Five occurred in 1927, 3 in 1928, 3 in 1929, 1 in 1930, 2 in 1931, none in 1932, 1 in July of 1933, and none for the past 8 months. The fractures (Figs. 5, 6 and 7) during this period of 7 years, usually occurred at the ends of the diaphyses. They have been of the simple oblique or transverse type. They have never been comminuted nor compound. "Foamy epiphyses" and mottling of the metaphyses are present.

Our recent roentgenographic study of this patient shows few sites of old fractures, since psathyrotic bone heals with little callus formation. Normal bone heals with abundant callus formation. This "remarkable reparative property" of psathyrotic bone may be but another manifestation of some fundamental deficiency. The great disproportion between the size of the epiphyses and the diaphyses is another striking feature, especially of the femora (Fig. 8). The epiphyses appear to be normal, save for obvious osteoporosis. The diaphyses present a concentric type of atrophy, *i. e.*, the shaft is slender, the cortex thin, and the marrow cavity narrow. The deformities of the long bones and ribs are varied.

The skull is characteristically shaped. The calvarium is moderately thin and presents some mottling. The occiput is unduly prominent. The facial bones are small and rarefied. Many of the teeth are chipped. The pelvis is asymmetrical, and presents a mottled appearance and a high degree of osteoporosis. *The bones of the hands and feet are relatively normal.* These bones have never been fractured.

Metabolic Studies. We have investigated the total calcium balance and the iodin and chlorid balances of this patient. In our calcium studies we followed, essentially, the principles set forth by Bauer and Aub.[22] Seven days prior to the calcium investigation, the patient was placed on a constant low calcium diet which he chose from Aub's table.[22] The daily fluid intake was kept at about 2000 cc. The salt intake and acid base values of the diet were kept constant. This was a low iodin and chlorid-containing diet. The patient was kept on this regimen throughout the 8-day period of investigation. The patient was attended by nurses trained in the conduct of patients during mineral metabolism studies. The urine was collected in 24-hour specimens. The feces were collected in 2 periods of 4 days each.

The serum calcium was determined by the Clark-Collip method.[23] Urinary excretion of calcium and water calcium were determined by the Shohl-Pedley method.[24] Determination of fecal calcium was essentially by McCrudden's titrimetric method;[25] an aliquot part of the feces being oxidized in silica at a low temperature with the aid of oxygen. The calcium content of food was calculated from Sherman's[26] and Aub's[22] tables. The serum phosphorus was determined by the Bell-Doisy method.[27] The Whitehorn method[28] and Harvey's modified Volhard method[29] were used to determine the blood chlorid and the urinary excretion of chlorid. The Phillips-Curtis method[30] was used to determine the blood iodin and the urinary elimination of iodin.

Results and Interpretations. Although we have presented the figures actually obtained (Table 1), the results can be more readily appreciated by an inspection of the graph (Fig. 10). These findings

TABLE 1.—CALCIUM STUDIES ON A LOW CALCIUM DIET.

Date.	Weight, kg.	Calcium.					Blood serum.	
		Urine, mg.	Feces, mg.	Output, mg.	Intake, mg.	Negative balance, mg.	Calcium, mg. %.	Inorganic phosphorus, mg. %.
10/22/33 . . .	20.4	142	168	310	175	135		
10/23/33 . . .	...	161	168	329	175	154	9.9	3.1
10/24/33 . . .	...	238	168	406	175	231		
10/25/33 . . .	19.4	134	168	302	175	127	10.5	2.5
10/26/33 . . .	...	139	104	243	175	68		
10/27/33 . . .	...	161	104	265	175	90	10.2	2.7
10/28/33 . . .	19.8	197	104	301	175	126		
10/29/33 . . .	...	166	104	270	175	95		
Average . . .	20.0	167	136	303	175	128	10.2	2.7

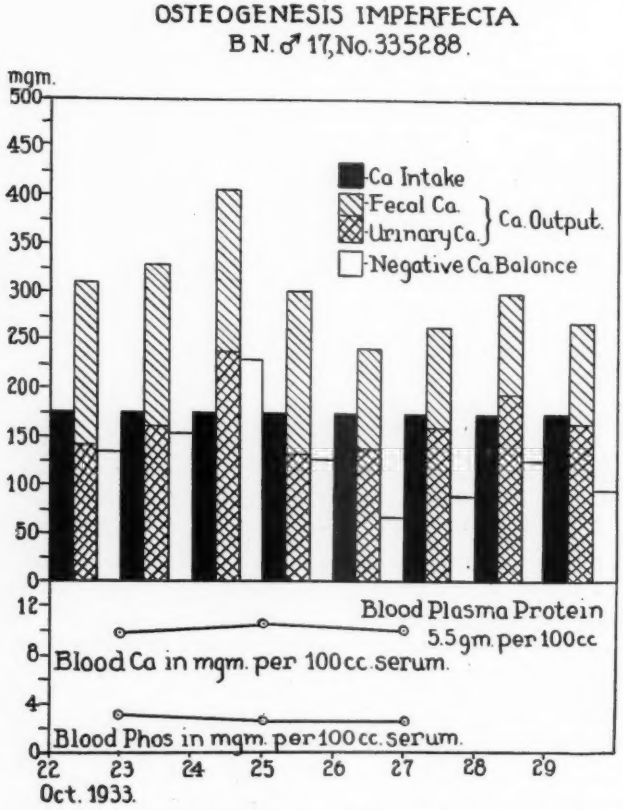

FIG. 10.—Graph of the calcium metabolism data from Table 1.

reveal no evidence of hyperparathyroidism. The serum calcium and phosphorus are normal. The urinary excretion of calcium is normal. The patient is in a continuous but normal negative calcium balance (Fig. 11).

The plasma chlorid averaged 310 mg.%, which is low normal. The daily urinary excretion of chlorid averaged 3.9 gm. This is within normal range for the low chlorid intake.

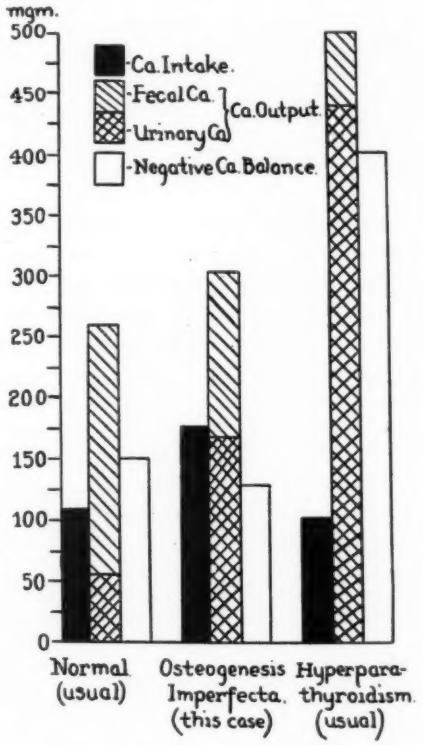

FIG. 11.—A comparison of B.N. with normal controls[22] and with a case of hyperparathyroidism.[21]

The blood iodin averaged 89 micrograms%, which is greatly increased. The daily urinary elimination of iodin averaged 101 micrograms, which is increased over normal. These facts concerning the iodin metabolism are submitted without any attempt at interpretation. They indicate an increase in thyroid activity.

Summary and Conclusions. 1. Osteogenesis imperfecta occurring in a young man of 17 is reported.

2. This patient exhibited the characteristic features of: Blue scleræ, increased bone fragility, a history of 50 fractures, dwarfism,

and marked deformity. There has been a decreased tendency to fractures since puberty. No fractures of the hands or feet have occurred.

3. His brothers present the typical blue scleræ. No other members of the immediate or remote family present blue scleræ or multiple fractures.

4. The calcium metabolism of the patient revealed no evidence of hyperparathyroidism. The serum calcium and phosphorus as well as the urinary excretion of calcium and the calcium balance were normal.

5. The blood iodin was increased. The urinary excretion of iodin was increased.

6. The plasma chlorid was low normal. The urinary excretion of chlorid was normal.

7. Osteogenesis imperfecta does not appear to be due to hyperparathyroidism.

8. It is suggested that this disease is due to a congenital hypoplasia of the mesenchyma, perhaps associated with a deficiency in bone phosphatase production. Further study of the latter is desirable.

BIBLIOGRAPHY.

1. Armand, J.: Quoted by Dry, T. J., Proc. Staff Mayo Clin., **8**, 329, 1933.
2. von Lobstein, J. F.: Traité d'anat. path., Paris, **2**, 204, 1833.
3. Henzschel: Ztschr. Ophthal., **1**, 52, 1831, quoted by Bell.
4. Cornaz, C. A. E.: Des abnormites congenitales des yeux et de leurs annexes, Lausanne, p. 67, 1848.
5. Bell, J.: The Treasury of Human Inheritance, Eugenics Lab. Publ., Univ. Coll., London, Memoir Series, No. 24, vol. **2**, pt. 3, 1928.
6. Fairbank, H. A. T.: Proc. Roy. Soc. Med., **23**, 1263, 1930.
7. Key, J. A.: Arch. Surg., **13**, 552, 1926.
8. Goin, L. S.: Am. J. Cancer, **17**, 668, 1933.
9. Bauer, K. H.: Deutsch. Ztschr. f. Chir., **154**, 166, 1920.
10. v. Recklinghausen, F. D.: Rachitis und Osteomalacia, Jena, Fischer, 1910.
11. Kraus, E. J.: Virch. Arch. f. path. Anat., **274**, 37, 1929.
12. Hennessy, J. P.: Am. J. Obst. and Gynec., **25**, 590, 1933.
13. Wagoner, G. W.: Ann. Surg., **80**, 115, 1924.
14. Wyatt, T. C., and McEachern, T. H.: Am. J. Dis. Child., **43**, 403, 1932.
15. Hunter, D.: Lancet, **1**, 999, 1930.
16. Hunter, D.: Ibid., **1**, 9, 1927.
17. Klercker, K. V.: Monatschr. f. Kinderh., **25**, 328, 1923.
18. Ryan, W. J.: J. Bone and Joint Surg., **14**, 939, 1932.
19. Robison, R.: Biochem. J., **17**, 286, 1923.
20. Kay, H. D.: Brit. J. Exp. Path., **7**, 177, 1926.
21. Crooks, J.: Brit. Med. J., **1**, 705, 1932.
22. Bauer, W., and Aub, J. C.: J. Am. Diet. Assn., **3**, 106, 1927.
23. Clark, E. P., and Collip, J. B.: J. Biol. Chem., **63**, 461, 1925.
24. Shohl, A. T., and Pedley, F. G.: Ibid., **50**, 537, 1922.
25. McCrudden, F. H.: Ibid., **10**, 187, 1911–12.
26. Sherman, H. C.: Chemistry of Food and Nutrition, New York, The Macmillan Company, 1933.
27. Bell, R. D., and Doisy, E. A.: J. Biol. Chem., **44**, 55, 1920.
28. Whitehorn, J. C.: Ibid., **45**, 449, 1921.
29. Harvey, S. C.: Arch. Int. Med., **6**, 12, 1910.
30. Phillips, F. J., and Curtis, G. M.: Am. J. Clin. Path., **4**, 346, 1934.
31. Bauer, W., Albright, F., and Aub, J. C.: J. Clin. Invest., **8**, 229, 1929–30.

SERUM PHOSPHATASE IN OSTEOGENESIS IMPERFECTA.

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A severe case of osteogenesis imperfecta was recently observed at the University Hospital (service of Dr. John Gittings) from birth until death 11 weeks later, and affords the opportunity of considering the serum phosphatase increase sporadically reported in this disease. In view of the preceding article[1] in this journal, repetition of other historic, clinical and pathologic discussion of the syndrome is superfluous.

In 1923, Robison[2] demonstrated in ossifying animal cartilage the presence of an enzyme ("phosphatase") capable of hydrolyzing phosphoric acid esters (such as are found in normal blood[3, 4, 16]) with the production of inorganic phosphate ions, which are readily precipitated by calcium from alkalin solution as complex inorganic salts. Its presence in cartilage which does not calcify, *e. g.*, tracheal cartilage, is not appreciable,[2] but its occurrence in other cartilage coincides with the appearance of the first ossification centers, as have been shown *in vivo*[5] and *in vitro*,[6] and its concentration varies with the rapidity of calcification, diminishing with age.[7] Upon immersion of rachitic bone in an alkalin solution of calcium glycerophosphate or hexosemonophosphate, fresh calcium salts are deposited.[7] For optimum activity, a temperature of 37° C., a pH of 8.4 to 9.4, and trace of magnesium in the substrate are necessary.[4, 7, 8, 11] Under laboratory conditions, the same enzyme is allegedly capable of esterifying inorganic phosphate in the presence of suitable alcohols (glycol, glycerol and hexoses).[9, 11]

Phosphatase is demonstrable in minute quantities in normal blood serum and corpuscles,[4, 10, 11] and is diffused throughout the tissues, but it is relatively concentrated only in the periosteum and epiphyseal zones of bone, in intestinal mucosa, and in kidneys (after acquisition of excretory function).[12, 13] Its concentration in serum is higher during childhood than in adult life,[4] physiologically increasing during the absorptive period of digestion, especially with carbohydrate food, and diminishing with post-hemorrhagic anemia, malnutrition or starvation.[14, 15] The enzyme is excreted by the kidneys at a rather constant rate, even when present in abnormal concentration in the blood.[12]

The biochemical assay of this enzyme depends upon the amount of phosphate liberated by hydrolysis of β-glycerophosphate under return to normal under adequate therapy a valuable guide in

standard conditions. Unfortunately, several modifications of the original method have created much ambiguity concerning the unit. The normal ranges for three of the best known methods are presented, but independent investigators[19] find more variation in the convenience of the technique than in the accuracy of the results.

NORMAL RANGE OF SERUM PHOSPHATASE (IN ARBITRARY UNITS).

Method.	*For Children.*	*For Adults.*
Kay[4]	0.17 to 0.34 Aver. 0.26	0.10 to 0.21 Aver. 0.15
Jenner and Kay[32]	.....	5.00 to 7.00 Aver. 6.00
Bodansky[21, 31, 33]	5.10 to 13.10 Aver. 7.30	2.00 to 3.50 Aver. 2.60

Normal blood contains phosphoric acid esters susceptible to the hydrolytic action of this enzyme,[3, 4, 16] as well as the ionized calcium and suitable alkalinity necessary for precipitation of complex calcium phosphate. Wells' concept[18] of ossification as a physicochemical precipitation of calcium carbonate and phosphate is now supplemented by this enzymatic release of phosphate ions at the site of ossification, the enzyme apparently being formed by the hypertrophic cartilage cells found there.[6] The selective affinity of bone for lead, radium and other similar metallic ions pathologically present is readily understood from this viewpoint. The phosphatase present in the kidneys apparently plays no part in the excretion of phosphate in the urine, which is regarded as an overflow of the inorganic phosphate present in the blood.[17] The rôle played by phosphatase elsewhere in the body, and the interpretation of abnormal concentration in the serum are subjects for speculation at the present time.

Kay and Robison, of England, and Bodansky and Jaffe, of New York, have studied the serum phosphatase in a variety of clinical conditions. Kay[12] feels that the deficiency of bone formation with abnormal softening permits a slow leakage of phosphatase into the blood, perhaps by being "squeezed out" of the pliable bone, and that the uniform rate of renal excretion permits a steady rise in the blood concentration of the enzyme. Bodansky and Jaffe[20, 21] object to this concept chiefly because of the ready physiologic fluctuation in normal individuals (*vide supra*), and believe that phosphatase variation is an expression of the capacity of bone for "cellular activities," associated with the formation of abnormal bone (Paget's disease) or osteoid tissue (rickets), and not with bone destruction *per se*.

Clinically, the concentration of serum phosphatase is found elevated (often 10 times normal) in obstructive jaundice (except in some anemic patients), and in generalized bone diseases (osteitis deformans, generalized osteitis fibrosa, osteomalacia, rickets).[12, 22, 23] The test has a practical application in rickets,[24] where the increase is an accurate index of the activity of the process, and its subsequent

treatment. In the other conditions the increase is usually of more academic than clinical value in the light of present knowledge.

We have found in the literature 23 cases of osteogenesis imperfecta (fragilitas ossium) that include serum phosphatase studies, age and sex of the patient; but very rarely is there specific mention of blue scleræ, otosclerosis, and ultimate outcome of the case. Any one of such factors might show some correlation with the inconstant moderate rise in phosphatase level. In addition, Hansen[27] mentions 3 cases, and Fraser[30] "several" with "normal" serum phosphatase, but with insufficient data for our tabulation here. Excluding 1 case with active rickets,[21] 8 of the remaining 22 patients showed a moderate elevation, ranging from 1.3 to 2.8 times normal average levels. Five of these 8 patients were in the 5- to 7-year age group, while 6 of them were female. Bearing in mind the "several" cases with normal phosphatase levels not included, an average twofold increase in serum phosphatase has been reported in less than 30% of the cases, chiefly between the ages of 5 and 7 years.

Hansen[27] has published the only report of phosphatase tissue distribution in this syndrome, based upon study of a 7-year-old girl, whose antemortem serum phosphatase level was "normal." He found a virtual absence of the enzyme in the periosteum and subperiosteal structures, and an extremely low concentration in the duodenum. In the blood and in other tissues no significant variation from normal values was demonstrated.

TABLE 1.—PHOSPHATASE VALUES IN OSTEOGENESIS IMPERFECTA (FRAGILITAS OSSIUM).

Reported by:	Diagnosis.	Age (yrs.).	Sex.	Serum phosphatase, Kay. Bodansky.	Degree of elevation.	Other factors.
Hunter, D.[25]	Osteog. imp.	42	M	0.162u	Normal	
Bodansky, A.[31]	Frag. ossium	38	M	2.4u	Normal	
Dry, T. J.[26]	Osteog. imp.	33	F	"Normal"	Normal	
Kay, H. D.[4]	Frag. ossium	27	M	0.16u	Normal	
Hunter, D.	Osteog. imp.	20	M	0.168u	Normal	
Hunter, D.	Osteog. imp.	17	M	0.331u	Normal	
Hunter, D.	Osteog. imp.	12	F	0.223u	Normal	
Hunter, D.	Osteog. imp.	9	M	0.27u	Normal	
Hunter, D.	Osteog. imp.	9	M	0.374u	1.4 × Normal	
Kay, H. D.	Frag. ossium	9	M	0.27u	Normal	0.33u 1 mo. later.
Kay, H. D.	Frag. ossium	7	M	0.54u	2 × Normal	
Hansen, A. E.[27]	Osteog. imp.	7	F	"Normal"	Normal	Autopsy studies.
Bodansky, A.	Frag. ossium	7	M	35.2u	5 × Normal	Active rickets.
Kay, H. D.	Frag. ossium	6	F	0.66u	2.5 × Normal	
Kay, H. D.	Frag. ossium	6	F	0.51u	2 × Normal	
Bodansky, A.	Frag. ossium	5	F	9.9u	1.3 × Normal	Anemia.
Bodansky, A.	Frag. ossium	5	F	19.1u	2.8 × Normal	
Bodansky, A.	Frag. ossium	3	M	7.0u	Normal	
Crooks, J.[28]	Osteog. imp.	2	F	0.30u	Normal	
Kleinberg[29]	Osteog. imp.	2	M	"Normal"	Normal	
Authors' case	Osteog. imp.	3 mos.	F	0.442u	1.7 × Normal	Anemia
Kleinberg, S.	Osteog. imp.	2 mos.	F	15.6u	2.2 × Normal	
Crooks, J.	Osteog. imp.	8 days	F	0.30u	Normal	

Case Report. A living female infant weighing 4 pounds and 8 ounces was born (spontaneous breech) April 17, 1935, after 5 hours' labor, the second child of a Wassermann negative 22-year-old white woman whose previous baby is normal and well, aged 20 months. In previous good health, the

mother was confined to bed 1 week during the first trimester of this pregnancy, suffering with a "nervous breakdown," and her diet throughout gestation has been apparently quite deficient owing to her aversion for vegetables and meat. Despite this her weight increased from 98 to 125 pounds. She first attended the prenatal dispensary in February, 1935, and was examined monthly thereafter without evidence of abnormality until her admission to the hospital in active labor 2 weeks prior to the expected date of confinement. No evidence of disease or deformity was discovered on physical examination, and her convalescence was entirely uneventful. Careful Roentgen studies of her entire skeletal system revealed no abnormality, and her serum calcium (10 mg. per 100 cc.) and phosphorus (4.1 mg. per 100 cc.) were within normal limits. The father has likewise enjoyed good health. An aunt and allegedly other more distant paternal relatives had blue scleræ, but neither brittle bones nor otosclerosis has been recognized among them.

The infant at birth presented the extensive deformities of the extremities that are shown in the accompanying picture. The head was large, the hair silky and rather abundant, and the ossification of the head was appreciable only in the temporal bones and in those composing the face. The cranium was likened to a "bag of skin," and the scleræ were decidedly blue. Many nodules were palpable through the thin subcutaneous tissue along the ribs, and a few subcrepitant râles were detected in the lungs. The heart sounds were of good quality, without murmurs, and no abnormalities could be demonstrated in the abdomen or genitalia. There was marked varus of the left knee and valgus of the right knee, accompanied by hyperabduction deformity of the right femur. The arms were in semi-abduction and flexion. The knee joints were partially ankylosed, and the elbows resistant to mobility. Preternatural movement was especially noteworthy in the right femur and the right humerus.

Roentgen studies revealed 14 fractures with much evidence of healing in the extremities, innumerable fractures of the ribs, and a general lack of normal radio-opacity of the bones. The urine and blood count were not abnormal, but a secondary anemia (71% hemoglobin, Sahli method) developed during the 3 months of life. The serum calcium (10.4 mg. per 100 cc.) and phosphorus (5.7 mg. per 100 cc.) were within normal limits, while the serum phosphatase determination (Dr. F. William Sunderman) of 0.442 unit (Kay) was 70% above the average normal and 30% above the upper limit of normal for infants.

The child was placed on an evaporated milk-Karo formula, but its weight never reached 5 pounds during the 11 weeks of life. Regurgitation of food and variable low fever without apparent cause were frequently encountered. The child was decidedly vegetative, lying almost motionless, and apparently unresponsive to sounds sufficient to elicit evidence of recognition in normal infants. Therapy was limited to vitamin preparations and daily sun-lamp irradiations. A temperature of 103° F. without recognizable cause occurred on the last day, but the child was unexpectedly found dead on July 7, 1935, aged 81 days.

Autopsy Findings. (No. 35-129, 14 hours after death by Dr. O. N. Smith.) The body was that of a moderately emaciated, deformed, female infant, weighing 2050 gm. The head was large, the face small, and the ears displaced somewhat caudally. The anterior calvarium was partially calcified, but flexible to palpation. The posterior aspect of the cranium was flattened and very soft. The anterior fontanelle was widely patent, and the sutures were not united, although the margins were in apposition. The hair was scant over the frontal region, but of fair growth over the parietal and temporal areas. The bitemporal circumference of the head was 33 cm., its

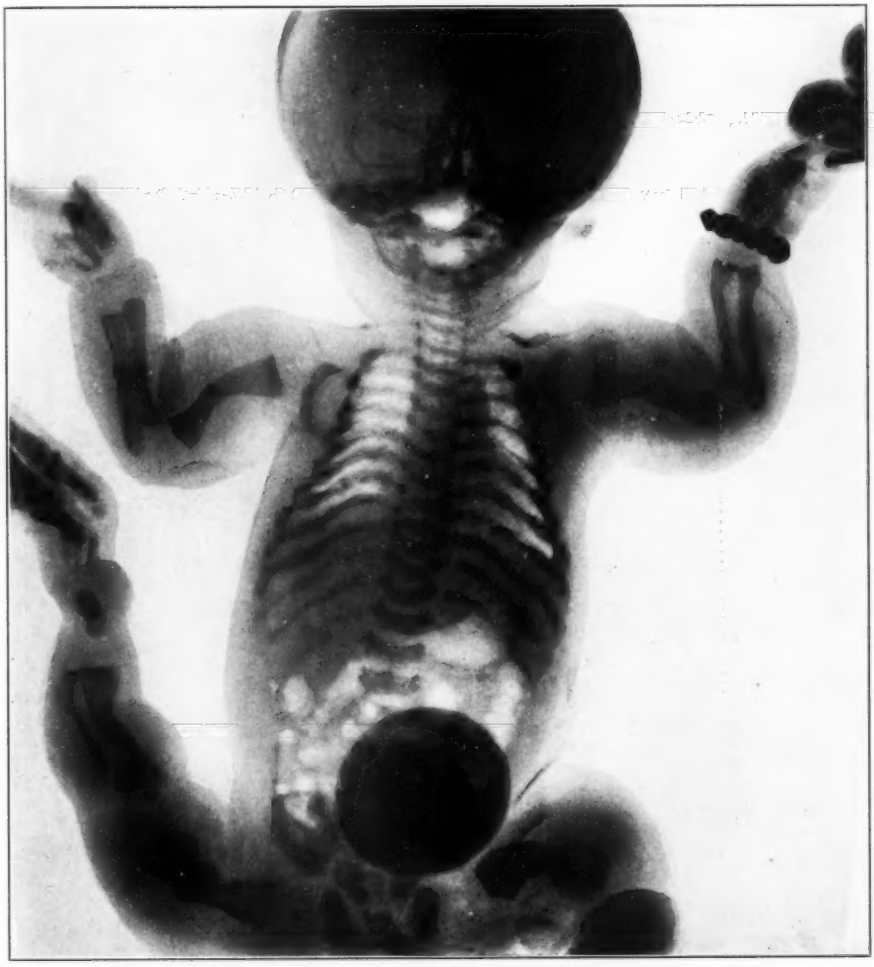

PLATE I.—Roentgen picture taken the day after birth, showing generalized rarefaction of bone, multiple fractures with marked callus formation, and extensive deformities.

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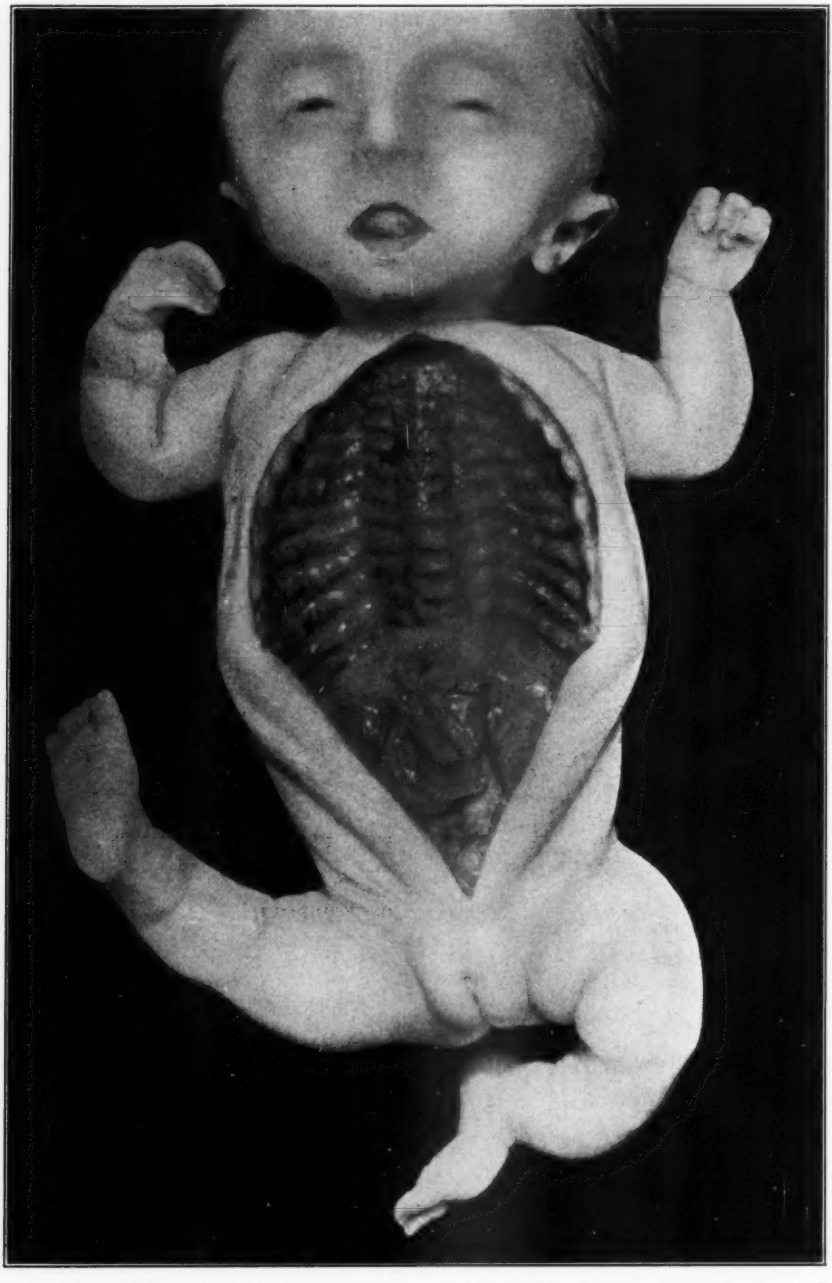

PLATE II.—Postmortem photograph of the patient, with thoracic contents removed, showing the beading of the ribs.

vertical height 12 cm., and the length of the trunk 20 cm. The deformities of the extremities were essentially the same as at birth, but preternatural mobility was no longer present.

Gross and microscopic study of the viscera (including the thyroid, parathyroid, thymus and adrenals) revealed no striking abnormality. There was microscopic passive congestion with slight edema of the lower lobe of the left lung. The ovaries were large, each measuring 10 by 6 by 4 mm., and contained several rather large follicle cysts. No brain lesion was found, nor could pus be demonstrated in the middle ears.

Pathologically, the skeletal lesions were of paramount interest. The occipital bones consisted of a mosaic of an uncountable number of small irregular fragments, simulating shattered eggshell, and diploic marrow was visible only in the anterior portion of the cranium. The ribs were irregularly beaded with 85 distinct nodules of callus, and each clavicle showed a single healed fracture. Including the 14 fractures of the long bones of the extremities previously noted, there was present a total of 101 fractures with evident healing. The bulk of the vertebral bodies consisted of cartilage, giving little resistance to the knife.

Microscopic study of stained (hematoxylin-eosin and Mallory's connective-tissue stain) sections from the vertebræ, ribs, femur, tibia and fibula showed the diaphyseal abnormalities described as characteristic of this disease. The periosteum was considerably thickened with fibrous tissue. The cortex presented an extremely thin, discontinuous osseous shell supported by uncalcified fibrillar substance, less dense and more cellular than the periosteum. The trabeculæ were diminished in number, imperfectly calcified, and sparsely scattered with little continuity; there was marked irregularity in lamellæ. The osteocytes were larger and much more closely packed than in normal bone. Many osteoblasts lined the margins of the trabeculæ, and were underlaid by a narrow pallid zone of uncalcified preosseous substance. Howship's lacunæ were rather sparse but large, the majority containing osteoclasts. In the ribs, the fractures were the seat of annular rings of uncalcified compact hyalin cartilage, appearing on cross-section as a subperiosteal wedge with the apex directed inward. In the long bones the fracture lines were marked by fibrillary healing, with definite increase in the number of trabeculæ bordering the zone of fibrous repair. The normal continuity of cancellous bone was nowhere evident, obviously as the result of numerical lack of trabeculæ, but the resemblance to normal was closer in the vicinity of these fractures.

Conclusions. 1. The origin, distribution and excretion of phosphatase and its rôle in normal individuals is briefly reviewed.

2. In the cases of osteogenesis imperfecta reported with serum phosphatase studies, an increase averaging about twice normal occurs in less than 30%, chiefly in patients between the ages of 5 and 7 years. In the remaining 70% the serum phosphatase was within normal limits.

3. This elevation is of more academic interest than of clinical value at this time, as its mechanism is not yet understood.

4. A severe case of osteogenesis imperfecta is presented, with notes on the clinical course (81 days) and autopsy findings. The serum phosphatase in one determination was 1.7 times the average normal level.

REFERENCES.

1. Puppel, I. D., Barron, L. E., and Curtis, G. M.: Am. J. Med. Sci., **190**, 756, 1935.
2. Robison, R.: Biochem. J., **17**, 286, 1923.
3. Martland, M., and Robison, R.: Ibid., **20**, 847, 1926.
4. Kay, H. D.: J. Biol. Chem., **89**, 235, 1930.
5. Martland, M., and Robison, R.: Biochem. J., **18**, 1354, 1924.
6. Fell, H. B., and Robison, R.: Ibid., **23**, 767, 1929.
7. Robison, R., and Soames, K. H.: Ibid., **18**, 740, 1924.
8. Bakwin, H., and Bodansky, O.: J. Biol. Chem., **101**, 641, 1933.
9. Kay, H. D.: Biochem. J., **22**, 855, 1928.
10. Kay, H. D.: Brit. J. Exp. Path., **10**, 253, 1929.
11. Roche, J.: Biochem. J., **25**, 1724, 1931.
12. Kay, H. D.: J. Biol. Chem., **89**, 249, 1930.
13. Kay, H. D.: Brit. J. Exp. Path., **7**, 177, 1926.
14. Freeman, S., and Farmer, C. J.: Proc. Soc. Exp. Biol. and Med., **31**, 536, 1934.
15. Bodansky, A., Jaffe, H. L., and Chandler, J. P.: J. Biol. Chem., **97**, lxvi, 1932.
16. Kay, H. D., and Robison, R.: Biochem. J., **18**, 755, 1924.
17. Brain, R. T., Kay, H. D., and Marshall, P. G.: Ibid., **22**, 628, 1928.
18. Wells, H. G.: Calcification and Ossification, Harvey Lecture, 1910–11, Philadelphia, J. B. Lippincott Company, p. 102.
19. Palmer, L. S., and Nelson, J. W.: Proc. Soc. Exp. Biol. and Med., **31**, 1070, 1934.
20. Bodansky, A., and Jaffe, H. L.: Ibid., **29**, 199, 1931.
21. Bodansky, A., and Jaffe, H. L.: Arch. Int. Med., **54**, 88, 1934.
22. Roberts, W. M.: Brit. J. Exp. Path., **11**, 90, 1930.
23. Bodansky, A., and Jaffe, H. L.: Proc. Soc. Exp. Biol. and Med., **31**, 107, 1934.
24. Bodansky, A., and Jaffe, H. L.: Am. J. Dis. Child., **48**, 1268, 1934.
25. Hunter, D.: Lancet, **1**, 999, 1930.
26. Dry, T. J.: Proc. Staff Meeting, Mayo Clinic, **8**, 329, 1933.
27. Hansen, A. E.: Proc. Soc. Exp. Biol. and Med., **31**, 1023, 1934.
28. Crooks, J.: Brit. Med. J., **1**, 705, 1932.
29. Kleinberg, S.: J. Bone and Joint Surg., **16**, 953, 1934.
30. Fraser, I.: Brit. J. Surg., **22**, 231, 1934.
31. Bodansky, A.: Proc. Soc. Exp. Biol. and Med., **28**, 760, 1931.
32. Jenner, H. D., and Kay, H. D.: Brit. J. Exp. Path., **13**, 22, 1932.
33. Bodansky, A.: J. Biol. Chem., **101**, 93, 1933.

(Titles have been omitted for sake of brevity.)

THE ELEVATED BLOOD UREA OF ACUTE GASTRO-INTESTINAL HEMORRHAGE AND ITS SIGNIFICANCE.

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The occurrence of elevated blood nitrogen figures in acute gastro-intestinal hemorrhage has received little consideration in recent medical literature, aside from the contribution of Sanguinetti,[1] which was published since the inception of this investigation. In the present report, 42 cases of hemorrhage due to peptic ulcer are analyzed, with particular reference to the presence of azotemia and its significance. The data are summarized in Table 1.

TABLE 1.—BLOOD CHEMICAL AND ASSOCIATED FINDINGS IN 42 CASES OF HEMORRHAGE DUE TO PEPTIC ULCER.

	Sex.	Age.	Urea.	H.*	Interval, acute hemorrhage to blood analysis.	
					3d or less.	More than 3d.
Group 1: 17 cases . . . Blood urea more than 38 mg. per 100 cc. . . .	M 14 F 3	28–68 Av. 49	40–103 Av. 58	21–96 Av. 60	14	3
Group 2: 25 cases . . . Blood urea less than 38 mg. per 100 cc.	M 18 F 7	17–63 Av. 39	Less than 38	20–95 Av. 53	4	21

Blood chlorids, uric acid, creatinin and alkalin reserve were within normal limits. A moderate leukocytosis and elevated blood sugar were usual in Group 1. All cases of both groups had normal blood pressure, negative urinary albumin and sediment and urine concentration of 1020 or better. No deaths.

While the maximum normal range of blood urea is from 10 to 50 mg. per 100 cc., most analyses fall between 18 and 38 mg.,[2] and consequently the last figure may be taken as the usual normal upper limit. Of the 42 cases studied, 17 (42%, Group 1) had blood urea over 38 mg. per 100 cc. Of these, 10 were over 50 mg. per 100 cc. Twenty-five (58%, Group 2) had blood urea well within normal limits and served as a control group for those with elevated nitrogen figures.

Neither sex nor age can be considered to be of significance in the causation of the abnormally high figures of Group 1, although the group with elevated urea averaged 10 years older than the normal group. No significant correlation between the degree of anemia *per se* and the azotemia was noticeable. In fact, the average hemoglobin of the normal group (53%) was lower than that of the azotemic group (60%).

When consideration was given, however, to the time relation between the occurrence of the hemorrhage and the taking of the blood samples for analysis, it immediately became apparent that the high nitrogen figures were found almost exclusively in those examined within 3 days of the acute episode. Thus, 14 of the 17 patients of Group 1 had suffered their hemorrhages within 72 hours of the taking of the blood samples (11 within 24 hours). Of the group with normal nitrogen figures, only 4 had their hemorrhages within 3 days; the remainder, anywhere from 3 days to several months before. Further, as would be expected, the first group as a whole is one of acute hemorrhage, usually with vomiting of considerable amounts of blood, and requiring immediate hospitali-

* H = Hemoglobin, Sahli.

zation. The second group is made up for the most part of chronic bleeders, although some had had a severe acute hemorrhage a long time before the taking of the chemistry.

The elevation of urea nitrogen in acute gastro-intestinal hemorrhage probably depends on several factors. Sudden blood loss in itself will cause an increase in the blood non-protein nitrogen figures,[3,4] as will shock.[5,6] These, of course, play a part in cases of gastro-intestinal hemorrhage, causing accelerated protein catabolism. Dehydration, too, will tend to raise blood nitrogen.[7] This factor was probably not negligible in the present series. Although gastric hemorrhage cases admitted to this hospital are routinely put on the diet recommended by Andresen,[8] in which an adequate amount of fluid in the form of gelatin solution is given, nevertheless the dehydration would hardly have been righted in the short interval before the taking of a blood sample. In this diet there is a significant amount of protein, but since the entire series was treated similarly, this cannot be considered a factor. The brief enforced starvation during the period of blood loss and dehydration may play a part,[9] although probably not as much with the Andresen as with other forms of treatment.

Impairment of kidney function probably was not concerned, as evidenced by normal blood pressure, good urine concentration and negative urinary albumin and sediment. Experimentally, kidney excretion of water is unimpaired by extensive bleeding.[10] Sanguinetti, too, does not consider that kidney dysfunction pays any part in the azotemia of gastro-intestinal hemorrhage.[1] With him we may feel that the most significant factor implicated is the appreciable quantity of nitrogen represented by the protein of the blood liberated into the gastro-intestinal tract. The absorption of this would cause a considerable elevation of the blood figures, particularly in cases where bleeding is continuous, although vomiting is not marked, and constipation is present as a result of morphin and the recumbent posture.

The azotemia of acute gastro-intestinal hemorrhage probably in itself plays little part in the clinical symptomatology, since it rarely reaches uremic proportions in cases uncomplicated by other adequate causes of elevated blood non-protein nitrogen figures. In this series, which is composed of uncomplicated cases, there were no deaths. In 1 case of cirrhosis and diabetes mellitus with very severe gastro-intestinal hemorrhage, due to a ruptured esophageal varix, there was definite uremia on admission, with a blood urea of 160. At autopsy this man had severe degenerative parenchymatous change of the kidneys. In uncomplicated cases, however, a urea above 102.7 was never noted, and uremia never played an appreciable part in the clinical picture. One can hardly, therefore, regard the azotemia with as much apprehension as Sanguinetti,

and certainly it does not seem that one would ever be driven to so drastic a procedure as cecostomy to insure the elimination of retained blood, as he suggests, should surgical intervention be indicated.

That determinations of the blood urea may have definite prognostic significance cannot be denied, as Duval and Grigant demonstrated in the instance of shock due to wounds[6] and as Sanguinetti and I have also observed in gastric hemorrhage. Thus, in the complicated case cited above, with persisting hemorrhage the urea rose to 246 before death. Similarly, in a fatal uncomplicated case, seen since the compilation of the data in this paper, the persistence of azotemia 1 week after the original chemical determination indicated continuing hemorrhage and presaged the patient's death. The fact that the elevated urea was not usually observed in cases seen more than 3 days after the acute hemorrhage agrees with Sanguinetti's observation that the maximum figures are attained on the third or fourth day. There is a rapid return to normal with cessation of hemorrhage. This was so in 2 cases reëxamined on the eighth and ninth days. It is probable, therefore, that a closer watch of the chemical composition of the blood in patients with gastro-intestinal hemorrhage who do not do well clinically may confirm the impression of persisting hemorrhage and may indicate the necessity for more radical, possibly surgical, treatment.

Dr. A. F. R. Andresen has brought to my attention Christianson's very recent report of 21 fatal cases of massive hemorrhage in peptic ulcer.[11] The general exhaustion which precedes death is considered to be on the basis of extrarenal hyperazotemia, preceded and accompanied by achloruria, rather than due to true anemia from persisting blood loss. This conception of the significance of uremia in gastro-intestinal hemorrhage is at variance with the impression gained from the uncomplicated, non-fatal cases reported here.

The urinary chlorids were not studied in any of the present series. Only 5 blood chlorid estimations were made (2 in Group 1; 3 in Group 2). These were normal. Nor was there any consistent abnormality in several alkalin reserve determinations made.

Of 4 fatal cases of gastro-intestinal hemorrhage, only 1, cited above, was uncomplicated. His urea did not go above 72 mg. per 100 cc. shortly before death from continuing hemorrhage. This could hardly have played any part in his death, although its persistence at this level in comparison with a previous chemistry was of prognostic significance.

Another, also mentioned above, had diabetes mellitus and hepatic cirrhosis with a ruptured esophageal varix. This patient continued to have terrific hematemeses and, although his urea climbed from 160 to 246, his blood loss was reasonably the major cause of death. Prior to death, he failed to concentrate above 1018 on 3 urine

examinations and an abnormal urinary sediment indicated the severe renal damage revealed at postmortem.

A patient with cirrhosis and ruptured esophageal varix continued to vomit blood until death. He failed to show even the usual azotemia of acute gastro-intestinal hemorrhage.

Another patient having duodenal ulcer with mild hematemesis showed a slight elevation of the blood urea at a time when the clinical picture was complicated by bronchopneumonia and jaundice.

These observations do not suggest that uremia plays any great part in the clinical picture of acute gastro-intestinal hemorrhage. The elevated blood nitrogen figures, *per se*, probably have no significant effect on the final outcome, except that, as already noted, persistent elevation may point to persistent hemorrhage.

Summary and Conclusions. 1. In cases of acute gastro-intestinal hemorrhage studied within 3 days of the occurrence of the hemorrhage, there is an elevation of the blood urea above normal. This is probably due to the nitrogen intake represented by the protein of the blood retained in the gastro-intestinal tract, plus the factors of hemorrhage, *per se*, shock, dehydration and starvation.

2. In uncomplicated cases this azotemia does not reach uremic proportions and plays little, if any, part in the symptomatology.

3. In cases with continuing hemorrhage the elevated urea persists or increases and points to an unfavorable outcome. The use of this diagnostic aid in cases which are not doing well may point to the necessity for radical intervention.

REFERENCES.

1. Sanguinetti, L. V.: Azoemias en el curso de las hemorragias retenidas a nivel del tubo digestivo, Arch. Argent. de enferm. d. ap. digest. y de la nutrición, **9**, 264, 1934.

2. Peters, J. P., and Van Slyke, D. D.: Range of Normal Blood Urea Content: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins, vol. **1**, Interpretations, p. 336, 1932.

3. Taylor, A. E., and Lewis, H. B.: A Study of the Protein Metabolism Under Conditions of Repeated Hemorrhage, J. Biol. Chem., **22**, 71, 1915.

4. Buell, M. V.: Studies of Blood Regeneration: II. Effect of Hemorrhage on Nitrogen Metabolism, Ibid., **40**, 29, 1919.

5. Aub, J. C., and Wu, H.: Studies in Experimental Traumatic Shock: III. Chemical Changes in the Blood, Am. J. Physiol., **54**, 416, 1920.

6. Duval, P., and Grigant, A.: L'intoxication par les plaies de guerre: La retention azotee des blessés, Compt. rend. Soc. de biol., **24**, 873, 1918.

7. MacKay, L. L., and MacKay, E. M.: Increased Blood Urea of Extrarenal Origin, Am. J. Physiol., **70**, 394, 1924.

8. Andresen, A. F. R.: Treatment of Gastric Hemorrhage, J. Am. Med. Assn., **89**, 1397, 1927.

9. Lennox, W. G., O'Connor, M., and Bellinger, M.: Chemical Changes in the Blood During Fasting in the Human Subject, Arch. Int. Med., **38**, 553, 1926.

10. Rachmilewitz, M.: The Effect of Rapid Loss of Blood on the Secretion of Water by the Kidneys, New York, International Press, Libman Anniversary Volumes, **3**, 959, 1934.

11. Christianson, T.: Uremia as a Cause of Death in Massive Hemorrhage from Peptic Ulcer, Acta méd. Scandinav., **85**, 333, 1935; Abstract, J. Am. Med. Assn., **105**, 88, 1935.

EFFECT OF ANTICOAGULANTS ON SEDIMENTATION RATE.

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Various anticoagulants in widely different amounts have been used in determining the sedimentation rate of red blood corpuscles (Table 1).

Table 1.—Various Anticoagulants Used in Sedimentation Tests.

Investigator.	Anticoagulant.	Amount.
Westergren[1]	3.7% sodium citrate	0.2 cc. to 0.8 cc. blood.
Linzenmeier[2]	5.0% sodium citrate	0.2 cc. to 0.8 cc. blood.
Hunt[3]	1.6% sodium citrate	0.5 cc. to 3.5 cc. blood.
Cutler[4]	3.9% sodium citrate	0.5 cc. to 4.5 cc. blood.
Jacobs[5]	5.0% sodium citrate	0.4 cc. to 1.6 cc. blood.
Plass and Rourke[6]	Heparin	1.5 mg. dry to 5 cc. blood.
Rubin and Smith[7]	Hirudin	1.0 mg. dry to 5 cc. blood.
Cooper[8]	20% potassium oxalate	3 drops, allowed to dry, to 15 or 20 cc. blood.
Linton[9]	Powdered sodium oxalate	14 mg. to 5 cc. blood.
Mathieu[10]	Powdered potassium oxalate	2 mg. to 1 cc. blood.

Johnson[11] found that dry potassium oxalate and dry heparin increased the rate of sedimentation; sodium citrate in concentrations ranging from 2.5 to 5% gave slight variations in the sedimentation rate. He failed to state the amounts of the first 2 anticoagulants used.

Walton[12] used 1 cc. of 3.8% sodium citrate to 9 cc. of blood. He states that many parallel experiments were made using various anticoagulants, such as potassium oxalate crystals, hirudin and heparin, but he gives no results, nor does he state the amounts used.

This study was undertaken to determine the effects of various anticoagulants in equimolecular and other concentrations, and the effects of using the anticoagulant dry, or with varying amounts of solvent, on more than one method. The Cutler (large and small tube), the Westergren and the Linzenmeier methods have been used. The anticoagulants used include sodium citrate, ammonium citrate, sodium oxalate, potassium oxalate, ammonium oxalate and heparin.

Since sodium citrate is used in the 3 above methods, it serves as the control. The formula is $2Na_3C_6H_5O_7.11H_2O$, and molecular weight is 714.3. Cutler used 3%, or 0.0042 gm. mol. per 100 cc.; this is 15 mg. to 5 cc. final volume, for the large tube (0.5 cc. solvent and 4.5 cc. blood), and 3 mg. to 1 cc. for the small tube (0.1 cc. solvent and 0.9 cc. blood). Westergren uses 3.7%, or 0.0051 gm. mol. per 100 cc.; this is 3.7 mg. to 1 cc. final volume (0.2 cc. solvent and 0.8 cc. blood). If 2.5 cc. is desired as the final volume, 18.5 mg. of citrate are used. Linzenmeier uses 5%, or 0.007 gm. mol. per 100 cc.; this is 10 mg. to 1 cc. final volume (0.2 cc. solvent and 0.8 cc. blood).

Table 2 shows the amounts of the various anticoagulants, which are equimolecular to the sodium citrate used in each method:

TABLE 2.—AMOUNTS OF ANTICOAGULANTS USED IN EACH METHOD.

Anticoagulant.	Mol. wt.	Cutler.	Westergren.	Linzenmeier.
Ammonium citrate, $(NH_4)_3C_6H_5O_7$	243.2	1.0214% 5.107 mg. to 5 cc.	1.2403% 6.202 mg. to 2.5 cc.	1.7024% 3.405 mg. to 1 cc.
Sodium oxalate, $Na_2C_2O_4$	134.0	0.5628% 2.814 mg. to 5 cc.	0.6834% 3.417 mg. to 2.5 cc.	0.938% 1.876 mg. to 1 cc.
Potassium oxalate, $K_2C_2O_4.H_2O$	184.2	0.7736% 3.868 mg. to 5 cc.	0.9394% 4.697 mg. to 2.5 cc.	1.2894% 2.579 mg. to 1 cc.
Ammonium oxalate $(NH_4)_2C_2O_4.H_2O$	142.1	0.5968% 2.984 mg. to 5 cc.	0.7247% 3.623 mg. to 2.5 cc.	0.9947% 1.989 mg. to 1 cc.
Heparin in 0.9% NaCl	...	1 mg. to 5 cc.	0.5 mg. to 2.5 cc.	0.1 mg. to 1 cc.

Human blood was used throughout. In the control by each method, the determination was made as described by each author. In the studies in which the amount of solvent was varied, the anticoagulant was used, dry, with half the control amount of solvent, and with twice the control amount of solvent. The amount of blood varied accordingly, in order to keep the final volume the same as in the control.

Only the Cutler (large tube) and the Westergren results will be reported in detail. Only the 1-hour readings will be given. Table 3 presents the results. The control serves as the minuend in each case, to arrive at the difference.

In the Cutler method, increase of solvent delays and decrease of solvent hastens the rate of sedimentation. Increasing the amount of anticoagulant (sodium citrate) tends to delay the rate. Ammonium citrate gives a slight increase in the rate; sodium oxalate has little effect unless used dry. Potassium oxalate has slight effect; ammonium oxalate hastens the rate. Heparin increases the speed of sedimentation unless the amount of solvent is greater than the control amount.

In the Westergren method, as with the Cutler, an increase of

TABLE 3.—SEDIMENTATION RATES WITH DIFFERENT ANTICOAGULANTS BY THE CUTLER AND WESTERGREN METHODS.

Anticoagulant.		Cutler method (large tube).				Anticoagulant.		Westergren method.			
Mg.	Cc. solvent.	No. of cases.	Control. (Mm.)	Experimental. (Mm.)	Difference. (Mm.)	Mg.	Cc. solvent.	No. of cases.	Control. (Mm.)	Experimental. (Mm.)	Difference. (Mm.)
Sodium citrate.						Sodium citrate.					
15.0	0	14	4.8	5.8	−1.0	18.5	0	30	6.5	9.4	−2.9
15.0	0.25 H_2O	5	4.8	5.1	−0.3	18.5	0.25 H_2O	10	7.0	9.3	−2.3
15.0	1.0	5	4.9	3.8	+1.1	18.5	0.75	4	6.5	5.4	+0.9
37	0.5	24	5.3	4.7	+0.6	7.5	0.25	12	6.9	9.4	−2.5
50	0.5	23	4.9	4.3	+0.6	25.0	0.5	22	5.3	5.5	−0.2
						37.0	1.0	5	4.4	2.1	+2.3
						47.5	0.5	20	8.7	5.9	+2.8
Ammonium citrate.						Ammonium citrate.					
5.107 (equimolecular, 1.0214%)	0.5	17	6.3	7.2	−0.9	6.2016 (1.2403%)	0.5	38	4.1	3.5	+0.6
7.5 (1.5%)	0.5	50	10.2	13.6	−3.4						
Sodium oxalate.						Sodium oxalate.					
2.814 (equimolecular, 0.5628%)	0.5	106	6.9	7.0	−0.1	3.417 (0.6834%)	0.5	36	3.5	2.9	+0.6
8.0	0	8	5.7	7.1	−1.4	0.64	0	5	1.7	2.6	−0.9
8.0	0.5	10	7.0	7.0	0	0.64	0.5	5	1.7	1.8	−0.1
8.0	1.0	5	3.2	2.8	+0.4						
Potassium oxalate.						Potassium oxalate.					
3.868 (equimolecular, 0.7736%)	0.5	34	6.8	7.4	−0.6	4.6971 (0.9349%)	0.5	50	7.4	7.4	0
8.0	0	4	4.9	5.4	−0.5	8.0	0	5	2.3	3.0	−0.7
8.0	0.5	5	5.0	4.7	+0.3	8.0	0.5	5	2.3	2.3	0
Ammonium oxalate.						Ammonium oxalate.					
2.984 (equimolecular, 0.5968%)	0.5	35	11.2	13.5	−2.3	3.623 (0.7247%)	0.5	36	7.6	8.2	−0.6
17.5	0	5	5.9	9.7	−3.8	15.0	0.5	5	7.6	7.5	+0.1
17.5	0.5	5	5.9	8.9	−3.0						
Heparin.						Heparin.					
1.0	0	20	5.3	7.7	−2.4	0.5	0	13	6.4	8.2	−1.8
1.0	0.5 NaCl (0.9%)	20	5.3	6.0	−0.7	0.5	0.5 NaCl (0.9%)	59	4.5	5.1	−0.6
1.0	1.0 NaCl (0.9%)	20	5.3	5.4	−0.1	0.5	1.0 NaCl (0.9%)	19	6.1	4.3	+1.8

solvent delays and a decrease hastens the rate of sedimentation, and an increase in the amount of anticoagulant tends to delay the rate. With ammonium citrate the rate is slightly decreased, contrary to the results with the Cutler method. Sodium oxalate gives a slight retardation; potassium oxalate has little effect; ammonium oxalate gives a slight increase in rate. Heparin increases the speed of sedimentation unless the amount of solvent is greater than in the control.

The results with the small Cutler tube were essentially the same as with the large Cutler tube. In the Linzenmeier method the results of varying the amount of sodium citrate and of varying the amount of the solvent were essentially the same as with the Cutler method. Ammonium oxalate and heparin hastened the sedimentation rate; the other anticoagulants were not tried.

Summary. Although the changes in the sedimentation rate are probably not great enough to affect the clinical results markedly, the following observations are interesting. Decrease in the amount of solvent hastens sedimentation; one can expect a faster rate when the anticoagulant is used dry. An increase in the amount of solvent beyond the control amount retards sedimentation, although the blood is diluted. An increase in the amount of anticoagulant, without change in the amount of solvent, tends to retard sedimentation. Ammonium citrate increases the rate in the Cutler and decreases it in the Westergren. Sodium oxalate, potassium oxalate and ammonium oxalate tend to increase the rate in the Cutler method, in the above order. The first decreased the rate in the Westergren, the second had no effect and the third increased the rate. Heparin increases the rate in all cases, unless used with a greater amount of the solvent than the control.

Conclusions. Sodium citrate is a highly satisfactory anticoagulant for use in the sedimentation test.

Fifteen milligrams in 0.5 cc. of distilled water, or 0.5 cc. of 3 per cent sodium citrate, is sufficient to prevent coagulation in 4.5 cc. of blood; this amount does not hemolyze the red blood corpuscles. A change either in the amount of anticoagulant or in the amount of solvent alters the rate of sedimentation.

REFERENCES.

1. Westergren, A.: Technique of Red Cell Sedimentation Reaction, Am. Rev. Tuberc., **14**, 94, 1926.

2. Linzenmeier, G.: Senkungsgeschwindigkeit der roten Blutkörperchen und ihre praktische Bedeutung, München. med. Wchnschr., **70**, 1243, 1923.

3. Hunt, H. F.: Studies of Sedimentation of Erythrocytes, J. Lab. and Clin. Med., **13**, 327, 1928.

4. Cutler, J.: The Graphic Presentation of Blood Sedimentation Test: Study in Pulmonary Tuberculosis, Am. J. Med. Sci., **171**, 882, 1926.

5. Jacobs, A.: Sedimentation Rate of Erythrocytes: Brief History and Discussion of Theories: Application in Gynecology, New Orleans Med. and Surg. J., **85**, 404, 1932.

6. Plass, E. D., and Rourke, M. D.: New Procedure for Determining Blood Sedimentation Rates, J. Clin. Invest., **5**, 531, 1928.
7. Rubin, E. H., and Smith, N. N.: Relation of Hemoglobin, Cell Count and Cell Volume to the Erythrocyte Sedimentation Reaction, Arch. Int. Med., **39**, 303, 1927.
8. Cooper, H. N.: Sedimentation Rate of Red Blood Cells, J. Lab. and Clin. Med., **11**, 615, 1926.
9. Linton, R. R.: Sedimentation Rate of Blood as Index of Hemorrhagic Tendency in Obstructive Jaundice, Ann. Surg., **91**, 694, 1930.
10. Mathieu, A., Trotman, F. E., Haskins, H. D., Osgood, E. E., and Albert, J.: Sedimentation Rate in Gynecology and Obstetrics: Results by Modified Westergren Technique in Over 2000 Determinations on 1100 Persons, Am. J. Obst. and Gynec., **21**, 197, 1931.
11. Johnson, F. B.: Sedimentation Rate of Erythrocytes, South. Med. J., **22**, 655, 1929.
12. Walton, A. C. R.: Erythrocyte Sedimentation Test, Clinical and Experimental Study, Quart. J. Med., **2**, 79, 1933.

TIGER-SNAKE VENOM IN THE TREATMENT OF ACCESSIBLE HEMORRHAGE.

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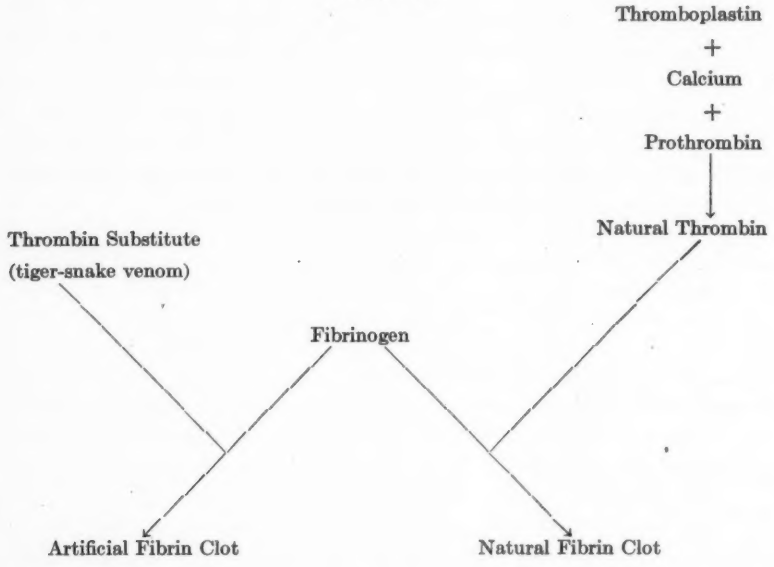
The dry venom of the Australian tiger-snake readily clots 12,800,000 times its weight of heavily citrated or oxalated blood. Whether this fantastic clotting power may be of clinical value in the treatment of hemorrhage has been the subject of the investigations which are presented herein.

It seemed to the authors that tiger-snake venom would be superior to other local hemostatic agents for the following reasons. First, it quickly produces a firm fibrin clot; second, it hastens the clot retraction; third, it does not require preliminary collaborating factors—thromboplastin, calcium, prothrombin—to coagulate the fibrinogen. The venom acting as a thrombin substitute requires only the presence of fibrinogen to form a clot (Fig. 1.)

Knowledge of this unusual power of tiger-snake venom is based upon experiments performed by many investigators during the past 42 years. Martin[1] in 1893 first demonstrated the activity of certain Australian snake venoms—Notechis scutatus, the tiger snake, and Pseudechis porphyriacus, the black snake—in causing the coagulation of blood *in vivo*. He showed that intravascular

clotting occurred quickly when a sufficiently large dose* was rapidly injected into the blood stream. However, when the dose was smaller, the blood after a brief period (a few minutes) of increased coagulability—the positive phase—partially or entirely lost its capacity to clot for many hours—the negative phase. When such blood in the negative phase was analyzed an absence of fibrinogen was noted; and the blood did not clot even if thrombin or coagulant venom in any quantity were added[2,3]. The blood did clot, however, when fibrinogen was added.[2]

FIGURE 1.



In 1905 Martin[4] working with tiger-snake venom confirmed the findings of Lamb[5] who had used the coagulant venom of another snake—the Russell viper of India. Martin found that minute doses of venom could coagulate *in vitro* blood which had lost the capacity for spontaneous coagulation on account of the addition of citrate, oxalate, or fluorid. He concluded that the coagulant venoms contained true fibrin ferments (thrombins). More recently Kellaway[6] made extensive investigations in the titration and pharmacologic action of various Australian venoms, stressing the very powerful coagulant action of the tiger-snake venom. In August, 1934, the writers, in a personal communication to Dr. Kellaway suggesting its use as a coagulating agent in hemorrhagic conditions, especially in hemophilia, procured from him a supply of tiger-snake venom with which to pursue clinical studies. In November, 1934, McFarlane and Barnett[7] using the coagulant venom derived

* 0.1 mg. (or more) intravenously for dogs, cats or rabbits.

from the Russell viper as a local hemostat, reported encouraging results in bleeding cases, including hemophilia; however no details of the treated cases were described. In 1935 Rosenfeld and Wiener[8] described a new method of determining quantitatively plasma fibrin, basing it on the coagulant activity of tiger-snake venom.

In Table 1 the snake venoms noted for their powerful coagulant action are listed, in order of their potency. Martin[4] regards tiger-snake venom as the most powerful, followed by the black snake, Echis carinatus, and daboia. Houssay and Sordelli[3] believe the Australian venoms to be the most active, followed by the Lachesis group, and after these the Vipera russellii. The exquisite coagulant activity of tiger-snake venom is also shown by the experiments of Kellaway.[6b]

TABLE 1.—SNAKE VENOMS HAVING A COAGULANT ACTION.

Family.	Genus and species.	Common name.	Habitat.
Colubridæ	Notechis scutatus	Tiger snake	Australia.
Colubridæ	Pseudechis porphyriacus	Black snake	Australia
Viperidæ	Echis carinatus	Phoorsa	India.
Viperidæ	Lachesis neuwiedii	Urutu	Brazil.
Viperidæ	Lachesis lanceolatus, or Bothrops atrox	Fer-de-lance	Tropical America.
Viperidæ	Vipera russellii	Daboia	India.

The venom of the tiger snake has been chosen for investigations for the following reasons:

1. Its clotting power is unexcelled.

2. Hemorrhagins (endotheliolysins) which produce local hemorrhagic extravasations are minimal in tiger-snake venom, whereas they are abundantly present in the Viperidæ, such as the daboia and the fer-de-lance (Kellaway;[6a] Calmette[9]). Calmette states that the venoms of the Viperidæ have a much greater local effect on mucous membranes than those of the Colubridæ, and may cause a severe acute inflammation with hemorrhages. When ingested orally large amounts of the venoms of the Colubridæ are innocuous, whereas those of the Viperidæ, especially the Lachesis group, provoke a violent gastritis, from which the animal may die.

3. Tiger-snake venom does not appear to render tissues unduly susceptible to bacterial invasion, as do venoms of the Viperidæ (Kellaway[6a]).

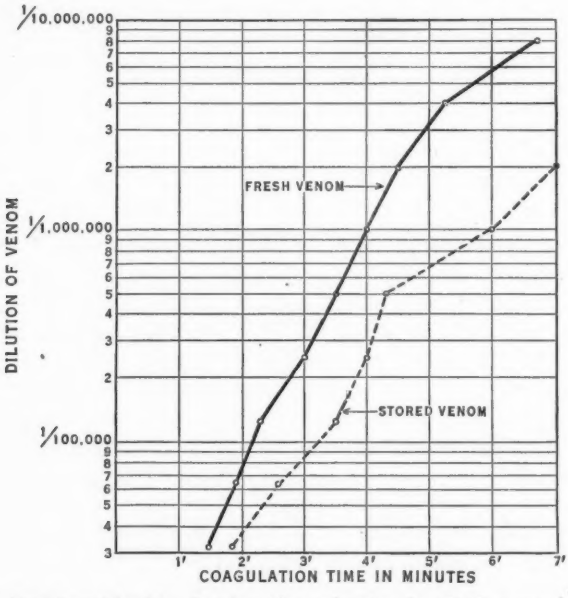
4. It has very little or no proteolytic action. On the other hand, Calmette[9] states that the coagulant venoms of the Viperidæ produce an intense proteolysis, even in weak solutions, so that the compact clots formed at first soon become soft and may then dissolve.

While it is true that the undesirable neurotoxin is more powerful in tiger-snake venom than in Viperidæ venoms, the minimal amounts of venom required and its action in closing the channels of absorption by local thrombosis, provide for tiger-snake venom a therapeutic index well within the limits of safety.

Preliminary Experiments. Preceding the clinical work, experiments were performed to assay the properties of the venom *in vitro* and *in vivo*.

A. *Titration of the Coagulant Power of the Venom.* A rack of tubes was prepared, each containing 0.1 cc. of progressive dilutions of venom in saline, each tube having $\frac{1}{2}$ the strength of the preceding one. The resultant titers extended from 1/1000 to 1/12,000,000. A control tube containing 0.1 cc. of normal saline was also used. To each tube was added 0.4 cc. of freshly drawn whole blood, rendering the final dilutions of venom 5 times as high as the original dilutions noted above. The coagulation time was measured with a stopwatch. Although the control blood required 8 minutes to clot, the venom caused firm clot formation within 1 minute up to a dilution of 1/320,000.

Using citrated or oxalated whole blood in a similar fashion, it was found that a final dilution of 1/160,000 venom produced a clot in 1 minute. It then became apparent that if plasma instead of whole blood were used, a nicer end point could be observed, the solution acquiring a whitish opacity



GRAPH I.—(Semilogarithmic), showing the reduction in clotting power of stored venom as against fresh venom.

just before clotting took place, thereby obviating the necessity of too frequent agitation. In all subsequent titrations, therefore, citrated plasma was used. Since the coagulation time of plasma was found to increase with its age, only fresh plasma was employed. All experiments were performed at room temperature.

Graph I represents the results of such a titration with freshly prepared venom, the ordinate representing dilutions of venom, the abscissa showing the coagulation time. The superimposed dotted line represents a titration of similar venom which had been stored for 2 months in the ice box at a dilution of 1/5000 in normal saline solution. The increased coagulation time shows that the clotting power of the stored venom has been moderately reduced by allowing it to remain in normal salt solution for 2 months.

B. *The Clotting Unit.* In an effort to standardize various batches of venom and to detect deterioration in stored solutions an arbitrary clotting

unit was devised. One clotting unit was defined as the clotting power present in the highest dilution of venom which will produce coagulation of freshly citrated plasma within 2 minutes,* the plasma being added to the various tubes of diluted venom in the proportion of 4 to 1 as described above. If the titration is so performed on an unknown solution of venom and if n represents the number of the last tube in which clotting occurs within 2 minutes, then a simple formula for the calculation of the units per cc. of unknown solution = $5 \times 2^{n-1}$. Tested in this way 1/5000 solutions of our various batches of tiger-snake venom proved to contain at least 7 units per cc.

C. *The Clotting Action on Pathologic Blood in Vitro.* Blood specimens were obtained and coagulation time by the Lee and White method were determined in the following cases.

TABLE 2.—CHANGES IN CLOTTING TIMES UPON ADDITION OF TIGER-SNAKE VENOM.

Hosp. No.	Disease.	Clotting time. Without venom (minutes).	Clotting time. With venom (seconds).
H. G. 154505	Hemophilia	(a) 5 (b) 12	(a) 50 (b) 50
B. L. 178536	Hemophilia	63	55
R. S. 178702	Essential purpura hemorrhagica (bleeding time more than ½ hr. Platelets = 2000)	7	50
O. S. 169638	Essential purpura hemorrhagica (bleeding time = 5½ mins. Platelets = 80,000)	4½	60
H. N. 178960	Acute myeloblastic leukemia (bleeding time = 20 mins. No platelets in smears)	10	45

These experiments demonstrated that *in vitro* the tiger-snake venom was efficacious in clotting the blood of patients suffering from active hemorrhagic disease. Most interesting was the observation that hemophiliac blood could be clotted as easily as normal blood.

D. *Animal Experiments.* The results of animal inoculation of the venom confirmed the observations of previous authors.

1. *Coagulant Action.* A series of experiments on cats showed that 0.5 mg. per kilo given intravenously produced death within 2 minutes. Autopsy revealed extensive intramuscular thrombosis. Intravenous injection of 0.1 mg. per kilo in cats caused death in 2 hours. Before this injection the clotting time of the cat's blood was 4 minutes; 15 minutes after the injection of venom another specimen of blood was withdrawn, which showed no tendency to clot after several days' observation. Even the addition of a large amount of venom failed to produce clotting. Autopsy of such "negative-phase" animals revealed fluid blood throughout the vascular tree except for a stringy thrombus in the portal vein.

2. *Hemorrhagin.* While intraperitoneal injection into mice of 1 cc. of 1/5000 solution (0.2 mg.) of moccasin venom produced a copious serosanguinous peritoneal exudate, no gross sign of peritoneal irritation was noted in the mice receiving an equal dose of tiger-snake venom.

3. *Neurotoxin.* Subcutaneous injection of 0.05 mg. per kilo. regularly killed rabbits within 24 hours, whereas intravenous injection of 0.005 mg.

* Coagulation within a period of 2 minutes was selected because: 1, It is the nearest approach to clinical requirements; 2, several tubes seem to clot almost simultaneously at about this time; 3, the more delayed clots are of poorer consistency.

per kilo regularly killed them within 15 minutes. A rapid method of estimating the neurotoxic potency of tiger-snake venom was that of subcutaneous inoculation of mice. Subcutaneous injection of 0.2 mg. regularly killed mice (weighing about 15 gm.) within 30 minutes, paralysis ascending from the hind-legs to the fore-legs, the heart continuing its pulsation for several minutes after respiration had ceased.

Preparation of Venom Solutions. The dried venom was pulverized, and 100 mg. lots were weighed out on a quantitative balance. Sterile normal saline solution was added to produce the required dilution, 1/100 volume of 1% merthiolate solution being included. The resultant saline solutions of venom (1/1000 and 1/5000 containing 1/10,000 merthiolate) were stored in the ice box for 2 days and then tested for sterility. Aërobic cultures on blood plates and glucose broth were made. Since anaërobic spore-bearing pathogens have been described in snake venom (Kellaway and Williams,[10]) each solution of venom was cultured anaërobically and also was injected in sublethal dosage (0.1 cc. of 1/5000 solution) into the hamstring muscles of a guinea pig. No contaminant was found after the routine treatment with merthiolate. Since sterilization by ultrafiltration or heat seriously impaired the clotting power of the venom, they were not employed.

The Clinical Use of Tiger-snake Venom in Hemorrhagic Diseases. The true evaluation of a hemostatic agent is hazardous. The study of a few carefully controlled cases is more valuable than any attempt to draw a mathematical deduction from numerous poorly controlled cases. The danger that spontaneous cessation of hemorrhage may be attributed to the therapeutic agent, or that the venom packing receive credit for hemostasis which plain packing alone could achieve, is especially to be controlled and avoided. Our conclusions will therefore be valued in direct relation to: 1, The length of time that hemorrhage had persisted unabated before venom is used; 2, the failure of simple packing to produce hemostasis; 3, the promptness of the response to venom.

Since normal patients did not bleed obstinately enough to satisfy the first two requirements, the investigations were limited to cases of severe hemorrhagic disease. Even these might have given specious results if the strict controls employed had not been diligently checked. Several patients with hemorrhagic diseases, not included in the appended reports, one a true hemophiliac with a coagulation time beyond 1 hour, stopped bleeding while the control treatments were being applied, before venom was used. As a general rule, venom was not used unless no diminution of the hemorrhage had been observed after sufficient trial of other common hemostatic agents.

Case Reports. CASE 1.—*Thrombocytopenic Purpura Secondary to Arsenic Poisoning.* S. G. (Hosp. No. 154505), male, aged 51, a furrier, with occupational exposure to arsenic dyes, was first admitted 3 years previously for pallor, tarry stools, and purpura of the skin. Anemia, thrombocytopenia, increased bleeding time, delayed clot retraction, and discovery of arsenic in the urine confirmed the diagnosis. During the following 6 months two episodes of severe hemorrhage after dental extraction occurred. During the past 2 years he has had sporadic hemorrhagic exacerbations, the gums

often bleeding for several days continuously. Pressure with plain gauze and with thromboplastin packings did not control the hemorrhage, blood oozing through the gauze for hours and even days until cessation occurred spontaneously or after transfusion. During an exceptionally severe exacerbation when the patient had bled continuously for 3 days from the gums with no decrease in the flow, tiger-snake venom was used. The blood findings at the time were similar to those described above. Systemic application of plain absorbent cotton and gauze packings, each held for at least 5 minutes against the bleeding area in the left lower gum, failed to check the flow. Systematic application of thromboplastin dressings were also futile, the blood oozing through the dressings. Finally after 1 hour of these control experiments, absorbent cotton wrung out in 1/5000 tiger-snake venom was pressed against the bleeding area. In 2 minutes bleeding had ceased. After an hour the venom pledget was removed, and copious bleeding recurred. Again thromboplastin and gauze packings failed to stop the flow and once more a venom pledget produced hemostasis within 2 minutes, the procedure being repeated several times. Undisturbed the venom pledget preserved hemostasis for several hours. When it was dislodged during mastication a fresh venom pledget immediately controlled the ensuing hemorrhage. The patient's disease, however, continued unabated, although the external hemorrhage was controlled, and he died suddenly 2 months later, of a cerebral hemorrhage.

CASE 2.—*Hemophilia.* H. G. (Hosp. No. 178039), male, aged 28, first admitted in February, 1935, gave a history of hemophilia, typical but for normal coagulation time. His maternal grandfather was a bleeder, and the patient was told that the "bleeding disease" was rampant in this grandfather's family. The patient has 2 brothers, 1 of whom is a bleeder. At circumcision, at tonsillectomy, and at tooth extractions, dangerous hemorrhage occurred, each one lasting for weeks. Three years ago he bled for 16 days after a slight laceration of his gum, requiring a transfusion. On admission blood examination showed a normal coagulation time (5 minutes by the Lee and White method), and the patient stated that the coagulation time had always been normal despite his bleeding episodes. The Howell prothrombin-time was 40 minutes, as compared to a normal control of 22 minutes. All the other hematologic tests were normal.

The upper left third molar was removed with novocain and adrenalin anesthesia, and the area curetted. The first bleeding occurred 8 hours later. An interdental gauze packing failed to stop the bleeding. Then tiger-snake venom was applied on cotton without pressure for 10 minutes. A clot formed quickly, but was dislodged by the pressure of the escaping blood. This procedure was repeated 3 times without success. Then a venom pledget was applied, and pressure was maintained for 10 minutes with a gauze packing between the locked jaws. Bleeding ceased within the 10 minutes. Patient was awakened 4 hours later by recurrent bleeding. Again venom with pressure stopped the flow within 10 minutes. Four hours later hemorrhage again recurred, being controlled within 5 minutes by a venom pledget covered by an interdental gauze pack. This time the jaws were prevented from separating during sleep by a firm Barton bandage. There was no further bleeding until 7 hours later when the packing, venom-pledget, and clot were deliberately removed. Bleeding then recurred and was immediately stopped with a venom pledget covered by an interdental pack. No further bleeding occurred for 36 hours, when a slow ooze started, controlled intermittently by plain gauze packing without venom. This was followed by a larger flow which did not yield to plain gauze packing, but was stopped by the use of venom in 3 minutes. On each of the next 2 days, one packing with venom was sufficient to control the ooze. Patient was discharged 9 days after extraction, with the wound healing very well.

Nine days after his discharge, the patient, quite enthusiastic about tiger-snake venom therapy, asked to be readmitted for the extraction of two other diseased teeth. With his permission elaborate controls of other hemostatic devices were planned before venom should be employed. The patient was unusually coöperative, and even in the face of copious hemorrhage and while his hemoglobin was dropping rapidly, he insisted that we methodically exhaust our control methods before resorting to venom therapy.

On March 18, 1935, under novocain and adrenalin infiltration anesthesia, the lower left first molar and the upper right lateral incisor were evulsed. In addition, an alveolar flap was made at the base of the incisor for removal of a cyst. Three hours after the operation a slight ooze began, lasted 12 hours, barely tinting the saliva, and subsided without treatment. No bleeding occurred on the second and third days. On the fourth day oozing recurred and increased for 9 hours. A series of plain gauze packings failed to control the flow, so a packing steeped in a supersaturated tannic acid solution in 95% alcohol was applied. The hemorrhage soon diminished, and within 30 minutes had ceased.

On the fifth day, after 9 hours of intermittent bleeding, increasing in spite of plain gauze compresses, tannic acid gauze with interdental packing and a Barton bandage again produced hemostasis within 30 minutes. Two hours later hemorrhage recurred, but after 3 hours of futile gauze packings similarly responded to the tannic acid application with pressure.

On the sixth day, after an hour of bleeding, an adrenalin sponge diminished the flow temporarily, but 1 hour later profuse hemorrhage began from the three operative sites. Each of these received packs medicated at different times with tannic acid, gallic acid, ferric chlorid, and adrenalin. The bleeding became serious in spite of these measures. Finally venom was applied with pressure to the lower molar socket, which was bleeding dangerously. Within 3 minutes the flow from this site had stopped. The other two bleeding areas continued to flow unabated in spite of the other expedients. One hour later venom compresses stopped these two hemorrhages within 3 minutes. The two tooth sockets did not bleed thereafter.

It was noted at this time that a precipitated black incrustation of tannic acid and ferric chlorid had formed over the incision in the gum. On the 7th and 8th days bleeding occurred from the incision sporadically. On 2 occasions it did not respond to venom therapy promptly, subsiding only after 30 or 40 minutes. On the ninth day venom stopped the bleeding from the incision promptly after other methods failed.

On the tenth day bleeding from incision became serious again. It proceeded for 10 hours in spite of venom and other drugs. Finally, the entire bleeding area at the site of the incision was carefully denuded of the leathery black incrustation which formed a coating over it. A venom packing was applied to the raw and vigorously bleeding surface, and the hemorrhage ceased within 3 minutes. No further bleeding took place from the incision until the 14th day when profuse hemorrhage recurred. Because of the patient's anemia no preliminary controls were employed at this time. Bleeding ceased within 2 minutes after the application of venom (after 2 hours of hemorrhage). On the 15th day an ooze stopped spontaneously in 10 minutes. On the 16th day after 30 minutes of profuse flow venom therapy was followed within 2 minutes by hemostasis. Except for a slight ooze on the 17th day which stopped spontaneously in a few minutes, no further bleeding had occurred when the patient was discharged on the 24th day after operation. All the operative sites seemed well healed.

Case 3.—*Multiple Hereditary Telangiectases.* B. D., male, aged 55, realtor (treated by Dr. B. Seligman), gave the following family history: His mother, 2 sons, 1 daughter, and 20 nephews and nieces had had repeated, profuse hemorrhages, chiefly from the nose, in some cases from the tongue,

never from wounds of the skin. A brother had died of severe epistaxis. Almost all of them had had the onset of bleeding in adult life; 1 began to bleed in childhood.

For the past 20 years the patient had suffered from nasal hemorrhages, occurring about 4 times a week, usually lasting 5 or 6 hours. Examination showed multiple, generalized telangiectases, anemia, positive tourniquet test, no purpura, normal bleeding and clotting times, normal clot retraction, normal platelet count, and no abnormal blood cells.

The nasal hemorrhages rarely had yielded rapidly to pressure alone. The repeated use of adrenalin and especially of thromboplastin packings had produced hemostasis scarcely more promptly than had simple pressure, cessation occurring in about ½ to 1 hour. Treatment of bleeding points with chromic acid had produced an increase in the frequency and severity of the epistaxis.

This patient, a relative of Dr. Seligman, has been using tiger-snake venom for 3½ months, without medical supervision, being in Florida during this period. Epistaxis has occurred with equal frequency since tiger-snake venom therapy was initiated. The patient reports, however, that the hemorrhages have invariably yielded within 3 minutes after applying the venom. The loss of blood has been minimal. His weight, pallor, and general physical condition have greatly improved.

CASE 4.—*Essential Thrombocytopenic Purpura.* O. S., (Hosp. No. 169638) female, aged 14, has suffered from epistaxis for 9 years, and for the past 5 years purpura of the skin has occurred intermittently. Hematologic studies of the past 4 years during the periods of exacerbation of her disease have revealed secondary anemia, thrombocytopenia, prolonged bleeding time, delayed clot retraction, and positive tourniquet test.

On March 18, 1935, the lower right first molar was evulsed under nitrous oxid anesthesia. The postoperative bleeding was easily controlled by simple gauze packing. Fifteen hours later profuse hemorrhage set in and penetrated the packings. Packings of supersaturated tannic acid in 95% alcohol failed to influence the flow. After 2 hours of bleeding, unchecked by pressure of plain or of tannic acid packings, a tiger-snake venom compress was employed, and the bleeding ceased within 10 minutes.

On the second day a less severe hemorrhage was controlled by a tannic acid compress in 1 hour. On the fifth day a slight ooze occurred but subsided spontaneously. No further bleeding appeared.

On April 22, 1935, this patient returned to have the first and second upper left molar teeth extracted under nitrous oxid anesthesia. With one of the teeth adherent granulomatous tissue was evulsed. There were also multiple lacerations of the surrounding gum. A slight ooze occurred after the operation, and steadily increased during the succeeding 4 hours in spite of packings of cotton and plain gauze. A venom packing greatly diminished the flow, but did not stop it entirely. When the packing was removed 20 minutes later a solitary bleeding point was noted from beneath an everted lacerated fragment of the lateral alveolar margin. The interdental packing that had been used served only to lacerate this fragment further and to prevent its contact with the venom pledget. Another attempt to place venom in contact with this bleeding point was successful, digital pressure being employed on the venom pledget at this point for 5 minutes. Seven hours later severe hemorrhage recurred, again from the protruding fragment on the alveolar margin. Another venom pledget was carefully applied against the replaced alveolar fragment, and digital pressure maintained for 5 minutes. At the end of this time the resultant clot had firmly fixed the venom pledget to the wound, so that digital pressure could be released. The pledget was then held in place with gauze packing and a Barton bandage was applied. There was no further bleeding.

CASE 5.—*Essential Thrombocytopenic Purpura.* R. S. (Hosp. No. 178702), female, aged 23, gave a history of purpura of the skin, epistaxis, and bleeding gums for the past 8 months. Almost continuous epistaxis had been present for 3 weeks on admission. Hemoglobin was 26% (Dare), platelets 2000, bleeding time more than 30 minutes, clot retraction absent, tourniquet test strongly positive, leukocyte count normal. A transfusion was given after admission to the hospital on March 19, 1935. For 2 days after admission epistaxis continued from both sides of the nasal septum anteriorly. A rhinologist called in consultation was unable to diminish the flow of blood with plain packing, tannic acid packing, or adrenalin compresses. Finally, tiger-snake venom was used in packing the nose, and the flow stopped within 3 minutes. No nasal bleeding occurred for 36 hours thereafter. Then the nasal bleeding resumed. The entire left side of the septum appeared to be bleeding. Packing of the anterior nares with venom compresses failed to control slight bleeding posteriorly, and blood continued to ooze into the nasopharynx. No postnasal packing was performed. On the right side of the nose marked bleeding from Kiesselbach's triangle was stopped 2 minutes after the application of venom. On the same day a hemorrhage occurred from an abrasion in the external auditory canal of the right ear, and could not be stopped with plain packing or with tannic acid packing. Application of a venom compress stopped this source of bleeding within 3 minutes.

On the following day slight postnasal oozing persisted on the left side. On the sixth day splenectomy was performed under ether anesthesia. Later, slight nasal hemorrhage recurred but was controlled with plain gauze packing. A slight ooze from the abdominal wound was also noted, but controlled by plain gauze pressure. The patient developed a postoperative pneumonia, multiple lung abscesses, empyema, and died 16 days after admission to the hospital.

CASE 6.—*Hemophilia.* D. T. (Long Island Coll. Hosp. No. 1722, available through the courtesy of Dr. Tasker Howard), male, aged 25. Two maternal uncles of this patient had died in childhood of hemorrhage resulting from trivial external injury. The patient's bleeding tendency began soon after birth at circumcision. Recurrent hemarthroses, hematuria, hematomata, and prolonged hemorrhages from slight lacerations have occurred since infancy. Coagulation time of the blood in the past had varied between 30 and 50 minutes, but on present admission it has been between 8 and 17 minutes. No other hematologic abnormalities have been noted.

On March 22, 1935, the lower right second molar tooth was extracted. One hour later an oozing began which persisted intermittently for 12 days in spite of thromboplastin packings (renewed every 3 hours), adrenalin compresses, tannic acid dressings, and even electrocautery of the socket. After 12 days tiger-snake venom was applied to the socket, which had been bleeding through thromboplastin packings steadily for the previous 5 hours without signs of abatement. The bleeding stopped within 2 minutes. Seven days later a moderate oozing from the socket was again stopped within 2 minutes by venom. On the next day an ooze responded to venom with equal facility. No further bleeding occurred. The wound healed well.

CASE 7.—*Carcinoma of Head of Pancreas With Profound Jaundice.* B. L. (Hosp. No. 178852), male, aged 42, had an external biliary fistula created by cholecystostomy 6 months previously for obstructive jaundice due to carcinoma of the head of the pancreas. Intermittent jaundice had recurred since the operation because of blocking of the biliary fistula.

On the day before admission on March 25, 1935, severe epistaxis began, from both nostrils. Inability to control the hemorrhage led to his admission to the hospital. After futile attempts to control the hemorrhage with tannic acid and adrenalin packings, venom packings were employed. The bleeding ceased within 2 minutes.

CASE 8.—*Angioasthenia, with leech-bite hemorrhage.* M. B. (Hosp. No. 177514), female, aged 34, gives a history of previous prolonged postoperative hemorrhages (after surgical corrections of poliomyelitis deformities), a pronounced tendency to bruise easily, and occasional epistaxis (the last one lasting for 1 hour 2 days ago). She shows a pituitary type of obesity, purpuric spots in the skin, a markedly positive tourniquet test, normal bleeding and clotting times, no thrombocytopenia, and no abnormal blood cells.

After an operation on the right knee for suppurative arthritis she developed a thrombophlebitis of the right femoral vein. To the swollen and painful right thigh 5 leeches were applied on April 9, 1935. When the leeches had dropped off 1½ hours later a continuous and increasing ooze appeared at the 5-leech marks. The blood from the leech wounds showed no tendency to clot, although blood drawn from the median basilic vein clotted normally. In spite of prolonged pressure with plain gauze dressings held in place with bandages and sand bags, the profuse flow persisted for 5 hours before local venom therapy was instituted. Venom compresses were employed on all 5 bleeding points. Complete cessation of hemorrhage occurred within 2 minutes. An hour later manipulation by the patient of the bandages dislodged one of the compresses, causing a recurrence of the flow. The blood which inundated the bandages and the bed now contained large firm clots. Reapplication of a venom compress again stopped the flow within 2 minutes. An hour later further manipulation of the bandages because of marked femoral pain aggravated by the pressure, stirred up a slight ooze of thick clotting blood, which subsided permanently with no treatment other than the application of moderate pressure.

Comment. Tiger-snake venom has been successfully employed to check uncontrollable local bleeding in 8 patients suffering from hemorrhagic tendencies, of which 3 cases were thrombocytopenia, 2 hemophilia, 1 of each multiple hereditary telangiectases, prolonged jaundice and angioasthenia with bleeding due to local action of hirudin from leech bites.

During the clinical experiments there were only 2 occasions when doubt arose as to the efficacy of the venom. On 1 occasion (Case 2) the failure seems to have been due to a thick coating of precipitated ferric chlorid and tannic acid, which interfered with the action of the venom. When this incrustation was removed and venom was applied to the raw bleeding surface, hemorrhage ceased within 3 minutes. On another occasion (Case 4) after the application of venom, a lacerated fragment of gum continued to bleed when the rest of the wound was dry. The ordinary interdental packing was serving only further to lacerate this fragment and to increase the hemorrhage from the site. The application of a venom pledget by digital tamponade to the exact point of bleeding promptly stopped the flow.

It has been interesting to observe a sort of rhythmic recurrence of the bleeding tendency in the hemophiliacs. After tooth extraction the socket is usually quite dry for 8 to 12 hours (the more so, of course, if adrenalin was mixed with the local anesthetic). Then after serious bleeding occurs and is checked by venom, it may recur about 24 hours later. In Case 2 bleeding recurred at about the same time in the afternoon for a number of days. Venom does not seem

to prevent recurrences of bleeding from the treated area after an interval of hours or days. Perhaps the renewed flow is due to actual trauma, such as chewing, or to the cryptic factors which influence the hemorrhage in a hemophiliac, or to the washing away or destruction of venom. To minimize the possibility of recurrent hemorrhage, pressure should be maintained over the site of bleeding for several hours after hemostasis has been attained. For dental hemorrhage a Barton bandage has been usually applied overnight.

Neurologic examination of these patients disclosed no evidence that the neurotoxin of the venom was doing any damage. Even in patients who received large amounts (15 to 30 cc. of 1/5000 solution) orally or intranasally, no impairment of the cranial nerves and no muscular weakness were noted.

Locally no swelling, ulceration, necrosis or infection was observed. The wounds healed normally.

Some confusion may arise between tiger-snake venom and the venom of the water-moccasin which has been used recently to prevent hemorrhage.[11] Moccasin venom is given intradermally or subcutaneously. Tiger-snake venom is to be employed only by topical application and is not to be injected.

Summary. 1. Tiger-snake venom in high dilution readily clots both normal and pathologic blood *in vitro*.

2. A simple arbitrary clotting unit is described in an effort to standardize various batches of venom and to detect deterioration in aging solutions.

3. In cases of active hemorrhagic disease, tiger-snake venom has produced prompt local hemostasis when common expedients (pressure, thromboplastin, tannic acid, adrenalin, ferric chlorid) have failed.

4. The minimal amounts of venom employed and its action in closing the channels of absorption by local thrombosis provide for it a therapeutic index within limits of safety.

5. It has not prevented recurrence of hemorrhage or otherwise affected the course of the hemorrhagic disease.

6. Its application is limited to accessible bleeding lesions, where it may be applied topically with pressure.

Conclusion. The venom of the Australian tiger-snake (Notechis scutatus) has been successfully employed by topical application to arrest severe hemorrhage from accessible lesions in 8 cases of blood dyscrasia.

REFERENCES.

1. Martin, C. J.: On Some Effects upon the Blood Produced by the Injection of the Venom of the Australian Black Snake (Pseudechis porphyriacus), J. Physiol., **15**, 380, 1893.

2. Mellanby, J.: The Coagulation of Blood. Part II. The Actions of Snake Venoms, Peptone and Leech Extract, Ibid., **38**, 441, 1909.

3. Houssay, B. A., and Sordelli, A.: Action des Venins de Serpents sur la Coagulation Sanguine, J. de Physiol. et de Path. Generale, **18**, 781, 1919–1920.

4. Martin, C. J.: Observations upon Fibrin-ferments in the Venoms of Snakes and the Time-relations of their Action, J. Physiol., **32**, 207, 1905.
5. Lamb, G.: Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India, New Series, 1903, No. 4 (cited by Martin).[4]
6. Kellaway, C. H.: (*a*) Some Peculiarities of Australian Snake Venoms, Trans. Roy. Soc. Trop. Med. and Hyg., **27**, 9, 1933, (*b*) Med. J. Australia, **1**, 764, 1929, (*c*) Ibid., p. 348.
7. MacFarlane, R. G., and Barnett, B.: Hemostatic Possibilities of Snake Venom, Lancet, **2**, 985, 1934.
8. Rosenfeld, S., and Wiener, A. S.: A New Method of Determining Plasma Fibrin, Proc. Soc. Exp. Biol. and Med., **32**, 788, 1935.
9. Calmette, A.: Venoms (Translation) John Bale, Sons & Danielsson, Ltd., London, 1908.
10. Kellaway, C. H., and Williams, F. E.: Investigation of the Toxicity and Sterility of a Commercial Preparation Containing Modified Snake Venom, Med. J. Australia, **1**, 581, 1933.
11. Peck, S., and Rosenthal, N.: Effect of Moccasin Snake Venom (Ancistrodon Piscivorus) in Hemorrhagic Conditions, J. Am. Med. Assn., **104**, 1066, 1935.

"TIGHT" (NON-REGURGITANT) MITRAL STENOSIS.

A CLINICO-PATHOLOGICAL STUDY.

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TIGHT (*i. e.*, non-regurgitant) mitral stenosis as a clinical condition has received little attention in the most modern and complete textbooks of cardiology, such as White's,[1] MacKenzie's[2], Vaquez's,[3] Eden's,[4] Romberg's,[5] and others being mentioned in most cases merely as a pathologic curiosity. The scanty clinical description of this entity may explain why these cases come so often unrecognized to the autopsy table, surprising the pathologist with the unexpected extremely narrow mitral ostium. In most instances the condition clinically is believed to be a severe pulmonary infection or even a pulmonary neoplasm. Our interest was primarily aroused by a case of tight mitral stenosis (reported by us several years ago[6]) where the pulmonary signs were prominent and the rheumatic nature of the disease hidden, for the auscultatory findings over the mitral valve were entirely negative. Only the electrocardiogram was of some help, showing a high bifid *P* wave which made Dr. H. Vesell suspect the possibility of mitral stenosis. In the past 5 years, in which we have paid especial attention to this clinical

picture, we have had 13 such cases coming to autopsy at this hospital, the first 9 of which we have analyzed for this study. Of these 9, 5 were correctly diagnosed antemortem.

A careful study of these 9 cases convinces us that the condition is encountered frequently and clearly enough, especially in hospital practice, to deserve an autonomous status. The pathologic findings are distinct and uniform, indicating that a common clinical picture is associated with the entity. A description of the clinical course of the disease and the criteria by which this type of mitral stenosis can be diagnosed antemortem is the subject of this paper.

Beginning with the final picture, as it were, we find at autopsy as the key characteristic of the condition a slitlike, fibrosed and calcified mitral valve, so stenosed that a thin probe passes through it with difficulty, and so hard that it rings at the touch of the knife. The shape of the mitral opening varies—often it is "buttonhole," sometimes funnel shaped, sometimes stellate—but in all cases it is extremely narrow. The term *tight* mitral stenosis is then a much more fitting one than the more limiting term, *buttonhole*.

The rest of the changes are all secondary to the marked stenosis of the mitral ostium. Because insufficient blood reaches the left ventricle through the narrowed valve to furnish normal amount of work, this chamber atrophies. In contrast the left auricle is very large, usually extends beyond the right border of the heart, and is often filled with thrombi. The right side of the heart, too, suffers from the extreme obstruction to the blood flow at the mitral valves and both the right ventricle and auricle are slightly hypertrophied and dilated. Quite distinctive of the condition is the fact that the cardiac lesions are almost uniformly accompanied by extensive pulmonary changes—pulmonary embolization, pulmonary infarction, pulmonary fibrosis, and sclerosis of the pulmonary artery (including at times the smaller pulmonary vessels).

The stenosis of the mitral valve is so marked at autopsy that it is immediately recognized as the cause of death, since the circulation cannot be maintained for any length of time through such an obstruction. This also means that a lesser degree of stenosis must have preceded the terminally severe narrowing. The exact pathologic state before the marked stenosis has occurred cannot be evaluated with certainty in our present state of antemortem examinations. The presence of a small, atrophic left ventricle would indicate, however, that the auricle at no time received a reflux of blood, *i. e.*, that functionally at least the mitral valve was stenotic and not insufficient. Clinically, too, the patient shows the persistent symptoms, the failure at compensation and the poor reaction to treatment which distinguishes the case of pure mitral stenosis from the milder one of double mitral disease (stenosis and insufficiency). These pathologic and clinical considerations allow us to assume with some reason that the lesion began as a pure mitral stenosis without

accompanying insufficiency, or at least with the stenosis predominating over the insufficiency and that recurrent inflammatory changes took place in the valve to bring about a greater narrowing of the ostium. Of course, the possibility cannot be absolutely excluded that in the milder degree of stenosis there was a temporary insufficiency. In the younger individual the change is probably inflammatory and is connected with recurrences of the rheumatic infection. In the middle-aged period and later in life the fibrosis and deposition of lime in the mitral valve forms part of the general sclerotic process, but careful pathologic examination always shows that these mitral valves have been previously affected by the rheumatic virus. The arteriosclerotic process then is superimposed on the rheumatic in older individuals. In any case once the fibrosis and calcification has narrowed the mitral valve sufficiently, irreversible decompensation sets in, treatment is of no avail, and the patient falls a victim to the mechanical block in the circulation.

A summary of the 9 cases upon which this concept of the disease is based follows.

Case Reports. CASE 1.—Miss I. M. (No. 47054), aged 21, admitted to the service of Dr. A. A. Epstein, March 15, 1932, died March 17, 1932.

History. The patient gave no history of rheumatic fever or other rheumatic manifestations. On routine school examination in September, 1928, she was told she had a heart murmur. Soon after this she suffered from exertional dyspnea, cough and blood-streaked expectoration for a period of 3 months. She was feeling fairly well after that until December, 1929, when she complained of chilliness, palpitation, and recurrent attacks of precordial pain, unrelated to exertion, radiating to the left shoulder, and lasting about 10 minutes. Pallor and weakness increased for several months, so that on first admission to this hospital in May, 1930, she was suspected of having subacute bacterial endocarditis. No definite evidence for this could be obtained however. She showed at this time (May, 1930) a mitral lesion and pulmonary congestion, and was discharged improved but not fully compensated. She failed to regain complete compensation in the 2 years that followed. Five days before the present admission she began to complain of cough, sharp pains in the lower chest and bloody expectoration, and had a shaking chill 3 days later.

Physical Examination. Temperature, 104°; pulse, 124, thin; Respiratory, 32; blood pressure, 85/50. The patient looked acutely ill, markedly dyspneic and cyanotic. There was dullness, diminished breath sounds and numerous moist râles at the right base. The heart was enlarged, the first heart sound short and snappy. A double mitral murmur and thrill were present at the apex. *P*2 was markedly accentuated. The liver was felt 2 fingers below the costal margin; the spleen barely palpable.

Laboratory Findings. Urine negative. White blood cells, 23,200; 91% polys. Electrocardiogram. Right axis deviation. Large, slurred *P* waves in Lead II.

Course. The temperature rose the following day to 106.4°. In spite of oxygen and supportive treatment, the patient developed pulmonary edema and died.

Clinical Diagnosis. Decompensated mitral valvular disease. Bronchopneumonia. Pulmonary edema.

Anatomic Diagnosis, Condensed (By Dr. A. Plaut). "Buttonhole" mitral stenosis. Marked dilatation of left auricle. Small left ventricle.

Hypertrophy and dilatation of right ventricle. Dilatation of right auricle. Terminal verrucous endocarditis of tricuspid valve. Atheromatosis of right coronary artery (slight) and of pulmonary arteries (moderate). No Aschoff bodies microscopically. Bronchopneumonia, right lung. Pulmonary edema.

Comment. In this case, about 2 years before exitus, the patient developed dyspnea on slight exertion and pulmonary congestion, without any recurrent infection. At first treatment would influence her more or less favorably, but did not bring about actual return to compensation. The periods of relief would become less and less frequent, and the pulmonary congestion and stasis more and more marked until a terminal bronchopneumonia complicated the mitral valvular disease and brought about the fatal outcome. Periodically the patient had pains simulating angina pectoris, a condition not uncommon in many cases of mitral stenosis, particularly where the left auricle is extremely enlarged, as pointed out by Morawitz.[7] This explains why the anginal syndrome is more often present in tight mitral stenosis, where the left auricle attains a marked degree of distention, than in other forms of mitral disease. It is reasonable to assume that the patient started with a pure mitral stenosis and progressed to an absolute stenosis, as evidenced by the small, atrophic left ventricle. The marked progressive narrowing caused damming back of the blood in the lesser circulation, and led to terminal bronchopneumonia and pulmonary edema.

Case 2.—Mr. S. F. (No. 59465), aged 23, admitted to the service of Dr. I. W. Held on November 24, 1933, died November 25, 1933.

History. The patient had scarlet fever during early childhood, and rheumatic fever at 10 years. At this time he developed aortic stenosis and mitral stenosis. He recovered sufficiently to go through college and qualify as a teacher. However, from the age of 11 until he took sick with terminal pneumonia, he complained of shortness of breath, frequent spasmodic cough and occasional expectoration of tenacious sputum. In addition to the valvular disease, he had signs of bronchitis and emphysema, but at no time any evidence of decompensation. About 6 weeks before admission the patient was ill with Type I lobar pneumonia. With the aid of serum, he recovered completely and was well enough to be permitted back to work by the fourteenth day. He continued well for about a month. The day before admission, however, he suddenly became very ill, developed fever, pain in the left chest aggravated by breathing, cough and expectoration of blood-streaked sputum.

Physical Examination. Temperature, 103°; pulse 100, thin; respirations, 32; blood pressure, 106/70. The patient appeared acutely ill, moderately cyanotic, somewhat drowsy. Breathing was rapid and difficult. Tracheal râles were heard coming from the throat. There were numerous moist râles throughout both lungs. The heart was enlarged, especially to the left, the apical impulse abnormally forceful. There was a presystolic and a systolic murmur at the apex, and a harsh systolic murmur in the aortic area, accompanied by a thrill. The second aortic sound was not heard, the liver and spleen not palpable. There was no edema.

Laboratory Findings. Urine and blood, negative.

Course. The patient's condition was critical from the start. He was digitalized and put under an oxygen tent; a phlebotomy of 500 cc. was performed—all to no avail. In 23 hours he died.

Clinical Diagnosis. Chronic cardiovalvular disease. Tight mitral stenosis. Aortic stenosis. Bilateral bronchopneumonia. Pulmonary edema.

Anatomic Diagnosis, Condensed (Dr. A. Plaut). "Buttonhole" mitral stenosis. Stenosis of aortic and tricuspid valves. Verrucous endocarditis of tricuspid valve (terminal). Hypertrophy of heart. Old and recent rheumatic carditis, as evidenced microscopically by large number of scars and Aschoff bodies. Multiple areas of bronchopneumonia. Obliterating bronchiolitis.

Comment. This case is included, although not showing the typical clinical picture of the terminal decompensation of tight mitral stenosis, because we believe that of the 3 valvular lesions this patient had, it was the "buttonhole" mitral stenosis which influenced to a large extent the course of the disease (even when he was fully compensated) and eventually caused the fatal termination. It was responsible for the patient's chronic recurrent pulmonary symptoms, such as frequent cough and dyspnea, and also the obliterating bronchiolitis. It is our impression furthermore that the bronchopneumonia terminated with fatal pulmonary edema in so short a time largely because of the "buttonhole" mitral stenosis, for there were no signs of toxicity or sepsis which would otherwise cause the fatal outcome. The recent Aschoff bodies might be interpreted as showing that a recurrent rheumatic carditis was likewise present. It is very likely however that if the tight mitral stenosis had not caused the bronchopneumonia to terminate fatally the patient would have developed acute rheumatic carditis, activated by the recent pulmonary infection, and would have given clinical signs of this later.

CASE 3.—Mr. I. G. (No. 58550), aged 29, admitted to the service of Dr. M. A. Rothschild, October 17, 1933, died October 19, 1933.

History. The patient had rheumatic fever with migratory joint pains 13 years ago. Eight years later he was refused life insurance because of rheumatic heart disease. He was nevertheless symptom-free until 1½ years ago when dyspnea and persistent cough set in, to be followed by edema of the legs 4 months later. These symptoms increased steadily. The patient had been under careful medical supervision and had received 1½ to 4½ grains of digitalis daily for 6 weeks prior to admission. In spite of this he remained decompensated. He noticed jaundice a week before, and blood-streaked sputum a day before admission.

Physical Examination. Temperature, 100.2°; pulse 98, fair; respiration, 32; blood pressure, 132/96. The patient was acutely ill, pale, dyspneic, orthopneic. His lips, ears and extremities were cold and cyanotic. The lungs showed dullness at both bases posteriorly with moist râles and diminished breath sounds. The cardiac apex was in the anterior axillary line in the 7th interspace. A loud systolic and rough diastolic apical murmur were heard; *P*2 was louder than *A*2; the rhythm distinctly coupled. The liver was felt pulsating 5 fingers below the costal margin. There was no evidence of ascites, although the extremities and scrotum were edematous.

Laboratory Findings. Urine 3+ albumin, with occasional granular casts. Blood and sedimentation rate normal. Circulation time 51 seconds. Electrocardiogram. High, wide, notched *P* waves in Leads I and II. Raised *RS-T* segment in Lead I. Occasional ventricular premature contraction.

Course. Phlebotomy brought temporary relief; but the patient had a sudden attack of extreme restlessness and dyspnea on the second day. He rapidly became pulseless, and within 3 hours died.

Clinical Diagnosis. Chronic cardiovascular disease. "Buttonhole" mitral stenosis. Relative tricuspid insufficiency.

Anatomic Diagnosis, Condensed (By Dr. A. Plaut). "Buttonhole" mitral stenosis. Dilatation of right ventricle and left auricle. Verrucous endocarditis of aortic valve. Chronic endocarditis of tricuspid valve. Atheromatosis of pulmonary vessels. Fibrosis of lungs.

Comment. In summary this patient presented the picture of persistent pulmonary symptoms and signs for almost $1\frac{1}{2}$ years, such as dyspnea, cough, bloody expectoration, and progressive decompensation with edema. Even though he showed clinical evidence of tricuspid insufficiency (jaundice, large liver) the opening up of the tricuspid valve did not relieve his dyspnea because it was largely due to persistent, progressive pulmonary changes, such as pulmonary fibrosis. The decompensation in this case was prolonged, the symptoms persisting in spite of careful treatment (digitalis, etc.). Note that the electrocardiogram showed very high, wide and notched *P* waves, a finding which may be related to sclerosis of the pulmonary vessels and fibrosis of the lungs.[8]

CASE 4.—Miss A. S. (No. 43510), aged 34, admitted to the service of Dr. M. A. Rothschild, September 2, 1931, died September 4, 1931.

History. The patient had rheumatic fever at 3, 10, 15, 22, and 26 years. She had no cardiac complaints until 5 months before admission, when she first experienced shortness of breath and palpitation on exertion. From that time she became more and more incapacitated. In the last month a cough productive of blood-streaked sputum appeared, and the feeling of tiredness became more prominent.

Physical Examination. Temperature, 100°; pulse 100, Corrigan; respiration, 32; blood pressure, 150/34. The patient was very cyanotic and dyspneic. Numerous moist crackling râles were heard throughout both lungs. The heart was markedly enlarged, especially to the left. A systolic and diastolic murmur were heard at the apex, and a soft diastolic murmur at the base. The liver was palpable and tender 5 fingers below the costal margin. Moderate pretibial edema and some clubbing of the fingers were present.

Laboratory Findings. Urine and blood negative.

Roentgen Ray. Markedly enlarged heart, with the contour of combined mitral and aortic lesions.

Course. The patient failed to respond to digitalis therapy. She died in her sleep rather suddenly the second morning after admission.

Clinical Diagnostic. Chronic cardio-valvular disease. Mitral stenosis and insufficiency . Aortic insufficiency.

Anatomic Diagnosis, Condensed (By Dr. A. Plaut). "Buttonhole" mitral stenosis, showing microscopically calcific deposits within hyalinized fibrotic areas. Acute and chronic verrucous endocarditis of mitral and aortic valves. Concentric hypertrophy of all chambers of the heart. Marked hypertrophy with moderate dilatation of left ventricle. Aortic insufficiency. Acute verrucous endocarditis of left auricle. Pulmonary artery sclerosis. Pulmonary fibrosis. Chronic passive congestion. Early cardiac cirrhosis of liver.

Comment. In this case although there were multiple valvular lesions present and even evidence of acute changes in the valves and left auricle, one can state definitely that the aortic regurgitant lesion in itself was not responsible for the sudden decompensation, or the fatal outcome. In fact it was the very tight "buttonhole" mitral stenosis with marked pulmonary congestion, pulmonary fibrosis, and pulmonary artery changes in a relatively young person which caused the sudden terminal cardiac failure. This case exemplifies the dictum that a double valvular lesion, once decompensated goes more readily to fatal termination than a single one, especially if one of the lesions is of the tight mitral stenosis type.

CASE 5.—Mrs. R. D. (No. 51586), aged 35, admitted to the service of Dr. I. W. Held, October 23, 1932, died October 26, 1932.

History. The patient gave no history of rheumatic fever. She knew of her heart disease for 5 years before admission, during which time she suffered almost constant dyspnea and some orthopnea. She also had occasionally attacks of chest pain with substernal discomfort. On the day before admission there was an acute onset of fever, chills, pain in the left chest, cough and bloody expectoration.

Physical Examination. Temperature, 101.6°; pulse 116, fair; respiration, 36; blood pressure, 108/60. The patient was markedly cyanotic. There were numerous rhonchi heard throughout the chest, with dullness and crepitant râles at the left base. The heart was enlarged, the sounds weak and distant. A presystolic rumble was heard at the apex. *P*2 was markedly accentuated and reduplicated, suggesting gallop rhythm. The liver was palpable 3 fingers below the costal margin. There was no edema.

Laboratory Findings. Urine 2+ albumin, occasional granular cast. Red blood cells, 3,700,000; hemoglobin, 68%; white blood cells, 47,200; 92% polys. Sedimentation rate 60 mm.% in 45 minutes. Sputum: Type IV of pneumococcus.

Roentgen Ray. Consolidation of central portion of left lung and base of right lung. Mitral configuration with congestion of lungs due to decompensation.

Electrocardiogram. Split *P* waves in all leads. Diphasic T_2 and inverted T_3.

Course. The temperature rose steadily; the consolidation spread until it involved the entire left lung. Exitus occurred on the third day.

Clinical Diagnosis. Chronic cardiovalvular disease. Mitral stenosis. Lobar pneumonia, left lung.

Anatomic Diagnosis, Condensed (By Dr. A. Plaut). "Buttonhole" mitral stenosis. Retraction of aortic valves with recent verrucous endocarditis. Dilatation and hypertrophy of left auricle and ventricle. Moderate hypertrophy of right ventricle. Old and recent endocarditis of the tricuspid valve. Fatty changes in myocardium. Rusty color of right lung. Cheesy tuberculosis of hilar lymph nodes. Red hepatization of almost the whole left lung with diffuse fibrinous pleuritis. Stasis in spleen and liver.

Comment. For about 5 years this patient suffered from dyspnea, orthopnea and occasional attacks of suffocation simulating asthma. These symptoms, uninfluenced by treatment, were due to the persistent pulmonary congestion, bronchitis and emphysema secondary to disturbance of the pulmonary circulation in tight mitral stenosis. When pneumonia set in toward the end, the unfavorable dynamics

of the heart due to the "buttonhole" mitral stenosis led rapidly to cardiac failure and death. The slight verrucous deposits on the aortic and tricuspid valves are terminal and as such are found at autopsy in many cases of cachexia, severe infections, etc. In this case the persistent symptoms and physical signs pointing to pulmonary embarrassment (such as the marked accentuation and reduplication of the pulmonic second sound at the base simulating gallop rhythm) suggested the clinical diagnosis of "buttonhole" mitral stenosis.

CASE 6.—Mrs. S. B. (No. 61630), aged 37; admitted to the service of Dr. M. A. Rothschild, February 23, 1934, died February 25, 1934.

History. The patient had an attack of rheumatic fever at 24. She had no symptoms until about 2 years ago when she noticed difficulty in catching her breath on exertion. There was an interval of relative well-being until 6 weeks before admission when the patient had pain in the left chest and an increase in her shortness of breath. One week before admission she noticed swelling of the legs, cough and bloody expectoration.

Physical Examination. Temperature, 100°; pulse 100, small; respiration, 46; blood pressure, 110/50. The patient was exceedingly ill, dyspneic, cyanotic and orthopneic. There was a loud, harsh systolic murmur in the third left interspace accompanied by a systolic thrill. A distinct systolic murmur was heard at the apex transmitted to the axilla; but no definite diastolic murmur. The first sound at the apex was short. Auricular fibrillation was present with an apical rate of 150 and a pulse rate of 100. At the left base there was an area of bronchial breathing, dullness and coarse, moist râles. The liver was palpable 4 fingers below the costal margin. There was pitting edema of both lower extremities and back.

Laboratory Findings. Urine, sedimentation rate and circulation time normal. Venous pressure 22 cm.

Electrocardiogram. *Q–R–S* complexes of low voltage in all leads.

Roentgen Ray. Effusion in lower portion of left pleural cavity with some deviation of the heart and mediastinum to the right. Heart shape that of double valvular disease with very marked left auricular enlargement.

Course. In spite of rapid digitalization, the rate continued to be high. Phlebotomy of 350 cc. as well as thoracentesis of 1000 cc. of dark brown fluid from the left chest were of no avail. The patient became wildly irrational and died on the third day after admission.

Clinical Diagnosis. Chronic cardiovalvular disease. "Buttonhole" mitral stenosis. Aortic stenosis? Aortic insufficiency? Pulmonary infarction.

Anatomic Diagnosis, Condensed (*By Dr. A. Plaut*). Old and recent rheumatic mitral endocarditis with "buttonhole" stenosis. Thrombosis of left auricle and right auricular appendage. Old and recent aortic endocarditis with insufficiency and stenosis. Hypertrophy of right ventricle. Distention of both auricles. Perivascular scars and occasional small Aschoff bodies in myocardium microscopically. Atheromatosis of pulmonary vessels. Emboli of lung vessels. Large infarct, left lung and lower lobe of right lung. Serofibrinous pleuritis. Infarcts of kidneys and spleen. Nutmeg liver.

Comment. As in many of our cases of "buttonhole" mitral stenosis, this patient had an additional valvular lesion—the double aortic. Roentgen ray, autopsy and clinical evidence all indicated however that the cardiodynamics were determined almost exclu-

sively by the tight mitral stenosis. Roentgenologically, the configuration was mitral, not aortic. Anatomically, the left ventricle was not enlarged as in cases of aortic valvular disease. Instead, the right ventricle and auricles were hypertrophied and the pulmonary arteries sclerosed. Clinically, too, the picture was typically mitral. The first symptoms were those of stasis in the lungs due to interference with the pulmonary circulation. After a period of relative well-being, progressive decompensation with pulmonary infarcts and general anasarca developed. The heart could have gone on for a long time without decompensation were it not for the "buttonhole" mitral stenosis.

CASE 7.—Mr. A. B. (No. 54102), aged 39, admitted to the service of Dr. I. W. Held March 9, 1933, died March 14, 1933.

History. The patient had chorea at 3 years. For the past 17 years he has had dyspnea on exertion and more recently orthopnea. He was able to continue work as an artist until 2 years ago when ankle edema developed. At this first admission to this hospital, the condition was diagnosed as mitral stenosis and insufficiency, auricular fibrillation, moderate decompensation. With rest and digitalis he improved considerably; the edema disappeared. At home, despite employment of salyrgan and digitalis, edema of the lower extremities would make its appearance from time to time. He tired easily, and was practically an invalid the last few months. The weakness and edema increased a few weeks before admission.

Physical Examination. Temperature, 99.6°; pulse 100, fair; respiration, 26; blood pressure, 120/70. The patient was a slightly orthopneic, dyspneic man, not appearing severely ill. The lungs were clear. A long systolic, and a short diastolic murmur with a snappy first sound were heard at the apex. *P*2 was accentuated and reduplicated. Auricular fibrillation was present with an apical rate of 120 and a pulse rate of 108. The liver was felt 4 fingers below the costal margin, tender and pulsating. There was moderate ankle and pretibial edema.

Laboratory Findings. Urine 3+ albumin, frequent hyalin casts. Blood and sedimentation rate normal. Venous pressure 14 cm. Circulation time 40 seconds.

Course. The patient appeared to be fairly comfortable. His edema failed to react however to intensive digitalization. On the fifth day he took a sudden turn for the worse, and complained of overpowering weakness and shortness of breath. He showed signs of rapidly increasing decompensation. Numerous râles were heard throughout the lungs, evidencing the onset of pulmonary edema, and 15 hours later he died.

Clinical Diagnosis. Chronic cardiovalvular disease. Tight mitral stenosis. Ball-valve thrombus of left auricle?

Anatomic Diagnosis, Condensed (By Dr. A. Plaut). "Buttonhole" mitral stenosis. Distention of auricles. Large thrombus in left auricle. Dilatation and hypertrophy of right ventricle. Atrophic left ventricle. Severe atherosclerosis of pulmonary arteries with sclerosis to lesser degree of smaller pulmonary vessels. Edema of lungs. Stasis in spleen, kidneys and liver.

Comment. Although on previous admission, due to the systolic murmur, this patient was believed to have both mitral stenosis and insufficiency, the entire clinical picture speaks for the predominance of the stenotic over any possible insufficiency lesion. The atrophic left ventricle indicates that the mitral stenosis must have been

"tight" from the start, and explains why the patient was never perfectly comfortable and had dyspnea on exertion for fully 17 years. When the stenosis became more advanced in the last 2 years of the patient's life, the edema became more prominent and did not respond to treatment. Auricular fibrillation finally led to a sudden termination as the result of auricular thrombosis.

CASE 8.—Mrs. A. Z. (No. 55771), aged 42, admitted to the service of Dr. M. A. Rothschild, May 29, 1933, died June 15, 1933.

History. In 1923, at 32 years, the patient had polyarthritis. She was not aware of any cardiac involvement until 4 years ago, when she had polyarthritis, fever and marked dyspnea. Since then she was never fully compensated, her legs being always edematous to a greater or lesser extent. She was able to do her household tasks with difficulty until 8 months before admission, when she developed dyspnea, orthopnea, weakness, and occasional attacks of severe precordial pain. These symptoms continued until admission.

Physical Examination. Temperature, 100°; pulse 80, poor; respiration, 30; blood pressure, 100/60. The patient was acutely ill, markedly cyanotic, dyspneic and orthopneic. The heart was enlarged to the left, and had a loud presystolic and systolic murmur at the apex, with markedly accentuated *P*2. The liver reached 8 fingers below the costal margin, was tender and pulsating. There was pitting edema of the lower extremities.

Laboratory Findings. Urine, blood and sedimentation rate normal. Venous pressure 20 cm. Circulation time 28 seconds.

Electrocardiogram. Sinus arrhythmia. Inverted T_1. Another electrocardiogram shortly before exitus showed a wandering pacemaker.

Course. The patient received large doses of digitalis and salyrgan; phlebotomy was performed several times—all to no avail. The patient died in about 2 weeks.

Clinical Diagnosis. Chronic cardiovalvular disease. Tight mitral stenosis.

Anatomic Diagnosis, Condensed (By Dr. A. Plaut). "Buttonhole" mitral stenosis. Hypertrophy and dilatation of right ventricle and left auricle. Small left ventricle.

Comment. It is known from the history that for fully 6 years after the first attack of rheumatic fever the patient was not aware of any cardiac symptoms. It is not possible to state whether the first rheumatic attack left the valves perfectly intact or, what we think more likely, that they were injured so mildly as not to have interfered with the cardiodynamics. The second rheumatic attack however probably caused marked narrowing of the mitral ostium. Because of this the patient was never comfortable for the 4 years to follow, and progressed uninterruptedly, uninfluenced by treatment, to a fatal decompensation.

CASE 9.—Mr. D. O. (No. 38482), aged 47, admitted to the service of Dr. A. A. Epstein, December 10, 1930, died January 8, 1931.

History. The patient had rheumatic fever at 27 and again at 41. One year after the second attack (5 years ago), he began to have occasional shortness of breath and ankle edema. He was hospitalized 4 months prior to the present admission because of attacks of nocturnal paroxysmal dyspnea and recurrent ankle edema. The findings then were mitral stenosis, aortic insufficiency and auricular fibrillation. He was discharged improved.

Although not completely compensated on 6 grains of digitalis daily, he felt fairly well until 3 weeks before admission when he began to have recurrences of his nocturnal attacks of dyspnea.

Physical Examination. Temperature, 100°; pulse 80, thin; respiration, 35; blood pressure, 116/72. The patient was very cyanotic, dyspneic and slightly jaundiced. His respirations were of asthmatic character. There were numerous rhonchi throughout the chest, and diminished breathing at the right base. The apex was seen and felt in the anterior axillary line. The first heart sound was snappy and associated with a systolic murmur. Auricular fibrillation was present with an apical rate of 180 and a pulse rate of 80. The liver was just palpable; the ankles slightly swollen.

Laboratory Findings. Urine, blood and sedimentation rate normal. Venous pressure 21 cm. The icteric index varied between 20 and 25.

Electrocardiogram. Auricular fibrillation. Marked splintering of *Q–R–S* complexes in all leads.

Roentgen Ray. Cardiac decompensation with pleural effusion at right base.

Course. The patient became less cyanotic, and the edema of the legs subsided during the first week (after salyrgan injection). On the eighth day, however, he had violent pains in the right lower chest, bloody expectortion and rise in temperature to 103°. There were clinical and Roentgen ray signs of infarction at the right base. Seventeen hundred and fifty cubic centimeters of serosanguinous fluid were removed by paracentesis from the infarcted area a few days later. Signs of pyopneumothorax developed rapidly. He became progressively more cyanotic, dyspneic and edematous until death ensued about a month after admission.

Clinical Diagnosis. Chronic cardiovalvular disease. Mitral stenosis. Pulmonary infarct with secondary pyopneumothorax, right side.

Anatomic Diagnosis, Condensed (By Dr. A. Plaut). "Buttonhole" mitral stenosis. Old and recent mitral endocarditis. Aortic valves drawn out by scar formation between the mitral valve, and the septum. Recent thrombus partly obliterating mitral orifice. Parietal thrombosis in both distended auricles. Hypertrophy of right ventricle. Purulent infarct in lower lobe of right lung with basal empyema. Adhesions at both apices. Old infarcts in spleen and left kidney. General stasis.

Comment. The postmortem findings indicate that the main brunt of the disease was in the mitral valve in the form of a tight mitral stenosis. The aortic valve showed evidence of chronic endocarditis, but not marked to any great extent. Neither a high pulse pressure nor Corrigan pulse were present to suggest that the aortic valvular disease had much to do with the disturbed dynamics of the heart. The clinical course after the second attack of rheumatic fever speaks for greater narrowing of the mitral stenosis that already existed, causing a decompensation which was only slightly influenced by treatment and progressed rapidly to a fatal terminaation. The narrowing in this case of fibrillation resulted in multiple pulmonary infarcts, one of which became infected and led to a purulent pleural effusion.

Comment. Description of "tight" mitral stenosis as a clinical entity encounters the difficulty that the valvular lesion is often in the background, and the pulmonary signs in the foreground. Still a careful clinical study of the case, taking into consideration the

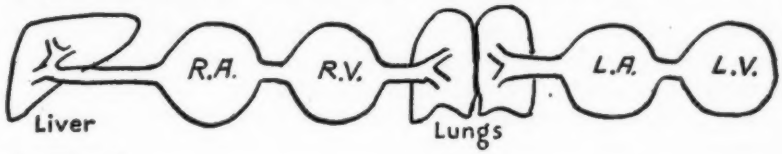
previous history, especially as regards circulatory status, should enable one to establish the proper diagnosis with the exception of those cases brought to the hospital *in extremis*, or where the pulmonary signs are so prominent as to mask entirely the underlying condition. That the diagnosis is possible is attested to by the fact that 5 of the 9 cases here reported were correctly diagnosed antemortem, as well as all of the 4 later cases not reported here. What are then the guiding diagnostic phenomena?

Since the condition starts as a mitral stenosis without an accompanying insufficiency, it is important to give the clinical characteristics of the pure mitral stenosis group, especially those which distinguish it from the more common double mitral involvement. We can thus learn to recognize those cases which are fertile soil for the development of a tight mitral stenosis.

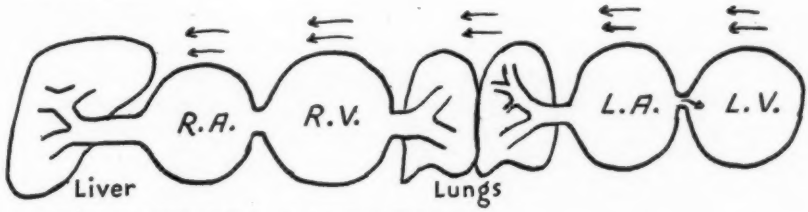
It is well known that in every mitral stenosis there is excessive strain on the left auricle and the pulmonary circuit, and a reduced blood inflow into the left ventricle. When insufficiency accompanies the stenosis, the narrowing is not as severe, and more blood reaches the left ventricle. The resulting hypertrophy of this chamber permits more blood to be pumped into the greater circulation, thus relieving any additional strain on the pulmonary circulation. In contrast in the case of pure mitral stenosis there is more narrowing and a greater strain on parts of the heart which are unable to bear the load, as Figure 1 shows. The blood reaching the left ventricle in these cases is so reduced in amount that left ventricle atrophy with consequent undernourishment of the heart and other body tissues results. This reduced left ventricular output shows itself clinically in the easy fatigability, the cold extremities, the thin pulse and the short snappy character of the first heart sound. Roentgen ray also shows *very early* in the course of these cases a mitral configuration with prominent pulmonary artery shadow, a dilated left auricle often extending so far to the right as to form the right upper cardiac border, and an enlarged right ventricle which pushes the small left ventricle outward to the left (Fig. 2). When the left auricle is much enlarged the barium-filled esophagus is found to be pushed to the right and also backward (by the anteriorposterior enlargement) as Brown and McCarthy have recently reported.[9]

The back-pressure chronic passive congestion which is part of all mitral disease is much more severe in the case of pure mitral stenosis than in double mitral affection. Because of its greater severity and persistence, chronic irreversible pulmonary changes, such as pulmonary fibrosis, pulmonary infarction, and sclerosis of the larger and smaller pulmonary vessels occur. According to Monterde,[8] the pulmonary hypertension with consequent arteritis is responsible for the high, bifid *P* waves which the electrocardiogram often shows in these patients. Clinically the severe pulmonary

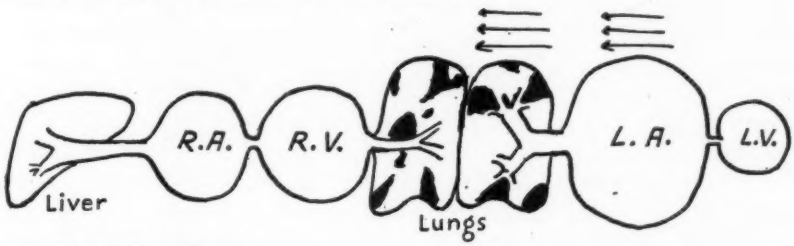
stasis is expressed as peristent pulmonary complaints and a markedly accentuated and reduplicated pulmonic second sound.



A. Normal.



B. Moderate Mitral Stenosis (+ Insufficiency).



C. Tight Mitral Stenosis.

FIG. 1.—Diagram illustrating the difference in the changes produced by moderate mitral stenosis with regurgitation and those of marked stenosis of the pure non-regurgitant type—tight mitral stenosis. The upper third (*A*) shows the normal relationship of the heart chambers to each other, and the pressure relationships in the lungs and the large venous bed of the liver. In moderate mitral stenosis (*B*) the left ventricle takes some of the load off the left auricle by regurgitation. The increased pressure in the left auricle is transmitted through the congested lungs to the right ventricle, which is consequently much enlarged. The load can further be taken off the enlarged right ventricle by the tricuspid valve which, becoming incompetent, permits the large veins and the liver to bear the brunt of increased pressure. In tight mitral stenosis (*C*) where no regurgitation is possible, the left ventricle does not relieve the load of the left auricle. In fact, it becomes atrophic from the insufficient amount of blood that it has to work on. The left auricle enlarges markedly, often 5 or 6 times its normal size. The pressure in the left auricle is tremendous, but cannot be adequately relieved by the lungs because of the numerous infarcts and thrombi forming in them. The lungs, instead of being elastic enough to transmit some of the pressure back to the right heart, must bear the brunt of the pressure itself, and become voluminous. This helps explain why the death in tight mitral stenosis is essentially a pulmonary one—and why once decompensated these cases offer no mechanism of recompensation.

We thus see that the patient with pure mitral stenosis does not do as well from the start as the average case of mitral stenosis with insufficiency. He is constantly troubled by "heavy chest colds," dyspnea on slight exertion, cough and blood spitting. The pulmon-

ary symptoms are usually so prominent that he is mistakenly believed to be suffering from bronchiolitis, chronic emphysema or even pulmonary tuberculosis. Occasionally the cardiac murmur cannot be heard at all, and only the pulmonary findings suggest the condition, as in the case of tight mitral stenosis reported by us several years ago which was clinically "silent."[6]

Though the patient with pure mitral stenosis is at a disadvantage as compared to one with mitral stenosis and insufficiency (whether absolute or relative from dilatation of the *A-V* ring), the prognosis is not hopeless. If the progress of the mitral lesion is halted it may be wide enough to permit adequate circulation for many years before decompensation ensues. Even then the decompensation is not necessarily irreversible or fatal, for the mitral ostium may be still physically large enough to permit sufficient circulation of blood. If however further inflammatory calcific changes take place, and a tight mitral stenosis is formed, the symptoms of marked pulmonary stasis become rapidly aggravated, and progressive irreversible decompensation sets in, often with pulmonary embolization, bloody expectoration, pulmonary edema, and terminal bronchopneumonia. The patient may still live a while longer, the burden on the lungs being somewhat relieved by the occurrence of right heart failure with relative tricuspid insufficiency and engorgement of the liver. The relief is only temporary, however, for the lungs have been permanently damaged by diffuse infarction, fibrosis, and secondary inflammatory changes.

The diagnosis of tight mitral stenosis, then, is made on the history of persistent cardiac and respiratory discomfort which does not permit the patient at any time to be fully compensated; the prominence of cardiac and pulmonary symptoms with scanty physical signs; and the rapidity and irreversible nature of the first true decompensation, which is also the last. In its clinical essence, the damage is mechanical more than inflammatory.

If the above picture and the possibility of the existence of the condition in any case of mitral disease which fails to react to treatment is kept in mind, the diagnosis will be seldom missed. There are very few conditions which simulate the profound decompensation of these cases toward the end. Pancarditis in a younger individual may occasionally appear like tight mitral stenosis, but in pancarditis the condition is essentially inflammatory, the sedimentation rate is increased, and signs of rheumatic activity are present. In tight mitral stenosis the decompensation is purely mechanical, being due to the block at the mitral orifice.

There is no way of ascertaining, unfortunately, which cases of pure mitral stenosis will later develop into tight mitral stenosis and which will not. However, any case of this kind showing persistent symptoms not noticeably relieved by the usual treatment (digitalis, bed rest) is probably already beginning to suffer fatal changes.

FIG. 2.—Early mitral configuration, simulating an egg standing almost on its end, showing a loss of the contours of the left border, prominent pulmonary shadow and enlarged right ventricle.

UNIV. OF MICH.

The dire consequences of the first decompensation in tight mitral stenosis emphasize the importance of reducing the activities of these patients. Although caution cannot prevent the further changes in the stenosed valve caused by reinfection, it can at least keep the patient from decompensating before the fatal narrowing occurs.

Conclusions. Tight (non-regurgitant) mitral stenosis is a definite clinical as well as pathologic entity. It is a fairly common terminal stage of pure mitral stenosis, *i. e.*, a stenosis without accompanying insufficiency.

The early stage is characterized by persistent symptoms of respiratory discomfort and pulmonary stasis—cough, dyspnea and acrocyanosis. There are only moderate signs of mitral disease—a short presystolic murmur, a click of the first sound, or a marked accentuation of the pulmonic second sound—so that these cases are often mistaken for primary pulmonary affections. The Roentgen configuration appears early and is typical of pure mitral stenosis. Due to sclerotic changes in the pulmonary artery the electrocardiogram often shows high bifid *P* waves.

The later stages of the disease are caused by inflammatory changes in the mitral valve with superimposed deposition of lime, which narrow the ostium still further, making it incompatible with life. Clinically this is marked by rapidly progressive, irreversible decompensation. The most prominent symptoms are pulmonary—persistent dyspnea and blood spitting. Often a bronchopneumonia complicates the terminal picture.

It is of both diagnostic and prognostic importance to differentiate this fatal type of mitral stenosis from the more benign form of double mitral disease (stenosis with insufficiency).

We are deeply indebted to Dr. A. A. Epstein and Dr. M. A. Rothschild who kindly allowed us to study and report 6 of the cases which were on their respective medical services, and to Dr. A. Plaut for his complete pathologic studies and helpful suggestions in these cases.

REFERENCES.

1. White, P. D.: Heart Disease, New York, The Macmillan Company, 1931.
2. MacKenzie, Sir J.: Diseases of the Heart, 3d ed., England, Oxford Univ. Press, p. 330.
3. Vaquez, H.: Diseases of the Heart, translated and edited by George F. Laidlaw, Philadelphia, W. B. Saunders Company, 1924.
4. Edens, E.: Krankheiten des Herzens und der Gefässe, Berlin, Julius Springer, 1929.
5. Romberg, E.: Krankheiten des Herzens und der Blutgefässe, 3d ed., Stuttgart, Ferdinand Enke, p. 288, 1921.
6. Held, I. W., Goldbloom, A. A., and Rittenberg, L. M.: Mitral Stenosis with Special Reference to Buttonhole Mitral Stenosis, Med. Clin. North America, **14**, 1311, 1931.
7. Morawitz, P.: Angina Pectoris, Verhandl. d. deutsch. Gesellsch. f. inn. Med. Kong., **43**, 278, 1931.
8. Monterde, F.: Das Elektrokardiogram bei Arteritis der Lungen Gefässe, Ibid., **45**, 433, 1933.
9 Brown, G. E., and McCarthy, J. E.: The Esophagus in Cardiac Disease, Radiology, **24**, 131, 1935.

ACTIVE VERSUS CONSERVATIVE MANAGEMENT OF PLANNED DELIVERIES.

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This report is a survey of contrasting methods and results of parturition in 3 maternity wards during identical periods of time in Philadelphia. Statistics of births from 1931 through 1934 are presented for the purpose of comparison with the tabulations of the Philadelphia Maternal Health Committee for these years, and because of definite change in recent obstetric practice featured by forceps control, episiotomy, labor analgesia, low Cesarian section, and a new conception of eclampsia. The material for consideration is the outcome of 5000 planned deliveries in the maternity wards of the Hospital of the University of Pennsylvania, the Methodist Episcopal Hospital, and the Preston Retreat of Philadelphia, to which is added a summary of 1500 private planned deliveries from a longer period of years.

Such comparisons might be misconstrued, but when offered by the same staff member from each service should be acceptable, particularly since this type of report is rarely available by reason of the fact that few annual hospital analyses segregate the results of planned from emergency deliveries. For example, prior to this review, in our obstetrical department, results of material from the receiving ward, consulting physicians, student outside service, and prenatal clinic have been hitherto grouped together in a general summary. Therefore it is timely to know the obstetric expectations of underprivileged mothers who have registered before and delivered after the 28th week of gestation in well-appointed maternity hospitals, following adequate prenatal care.

University of Pennsylvania Maternity.* This service received a large proportion of non-pay, many part-pay and some full-pay patients, including 33.8% colored women, most of whom were discharged 12 days after delivery. Under the late Professor Piper, there were 3 interns, 1 resident in obstetrics, 3 assistants (one at a time for 2 months), and myself as alternate obstetrician. Some of the material was used in the regular semiweekly teaching clinics, but most of these deliveries were witnessed, but not examined internally, by 1 or 2 students.

Causes of Maternal Deaths. 1, Postpartum hemorrhage after breech birth and tamponade of uterus; 2, postpartum hemorrhage after mid forceps; 3, postpartum hemorrhage after version; 4, post-

partum hemorrhage after twin birth; 5, septicemia, peritonitis after twin birth; 6, septicemia, peritonitis after high forceps; 7, septicemia, peritonitis after section for ectopic gestation; 8, septicemia, peritonitis; 9, myocardial failure; 10, nephritic toxemia after Cesarian section; 11, "labor pains"—shock during labor; 12, acute dilatation of heart after spontaneous delivery; 13, "collapse" after version.

* TABLE 1.—RESULTS OF PLANNED DELIVERIES.
Over 28 Weeks Gestation.

Description.	Univ. of Pennsylvania Maternity.	Methodist Hospital.	Preston Retreat.	Personal.
Total deliveries	2157	1070	2066	1472
Total operative interference	887—41.8%	169—15.8%	174—8.4%	823—56%
(Spontaneous)	1270—58.6%	901—84.2%	1892—91.6%	648—44%
Forceps	707—32.7%	118—11%	52—2.5%	636—43.4%
High-	3	3	0	20
Mid-	190	27	13	52
Low-	514	88	39	565*
Breech	61—2.8%	25—2.3%	91—4.4%	30—2%
"Spontaneous"	29	15	84	17
Extraction (decomposition)	4	1	1	13
A. C. H. forceps	29	9	6	22
Podalic version	42—2%	7—0.6%	16—0.8%	79—5.3%†
Cesarian section	76—3.5%	19—1.8%	15—0.7%	78—5.3%
Other complications:				
Surgical inductions	18	8	4	79—5.3%
Placenta previa	0	4	9	10
Complete lacerations	1	5	5	?
Eclampsia (no deaths)	6	3	7	3
Total morbidity	369—17%	114—10.6%	178—8.6%	7.9% (incomplete)
Spontaneous deliveries	11.1%			
High forceps	0			
Mid forceps	31.5%			
Low forceps	17.2%			
Maternal deaths (see causes)	13—0.6%	2—0.19%	3—0.14%	3—0.2%
Infant deaths (no corrections)	88—4.0%	30—2.8%	49—2.3%	37—2.6%
Stillborn	2.8%	....	1.4%	
Neonatal deaths	1.2%	....	0.9%	

* Mostly control.

† Including decomposition of 14 twins.

Comment. The forceps incidence is high but represents chiefly forceps control applied with the "head on the perineum" or scalp showing, inherited through a custom of 40 years from the Emeritus Professor of Obstetrics, B. C. Hirst. The total operative interference in 1934 for planned deliveries was only 14.5% lower than for the total average of 47.7% for *all* types of births during the previous 3-year period; but our 4-year maternal mortality of 0.6% is less than one-half that of 1.64% for the previous 3-year general rate reported by the Philadelphia Maternal Mortality Committee.

The University morbidity figures argue strongly for spontaneous delivery, in spite of absence of fever in the few cases of high forceps, which latter were performed by staff members.

No deductions or corrections are given under stillborn and neo-

natal deaths, in spite of the fact that the University Maternity syphilis frequency averages about 6%, and several monstrosities were included in this group. Forceps control should reduce infant death rate, but apparently failed to do so in comparison with the two other services, even though Foregger and Flagg apparatuses for insufflation of 10% CO_2 in 90% oxygen, and a respirator were available.

Analgesia may have accounted for some of the fetal deaths, since morphin and scopolamin or Gwathmey's rectal ether were utilized in the majority of labors, with nitrous oxid-oxygen anesthesia at delivery.

In normal as well as operative births, the management of the third stage of labor is a great source of morbidity or even mortality. In 4 of the University maternal deaths due to postpartum hemorrhage, and 3 due to sepsis, mismanagement of the placental delivery was a factor. It is possible that the plan of routine medication, namely, Ernutin mil. 0.5 intramuscularly at delivery of the infant, and Pitocin mil. 0.5 hypodermatically at delivery of the placenta, might have been related to the occurrence of postpartum hemorrhage; but it is certain that ceaseless simple holding-down of the fundus (particularly following deep etherization as for podalic version) until return of good after-contractions before expression of the placenta is vital.

Methodist Episcopal Hospital Maternity.* During the first 3 years of this survey all of the patients were obliged to pay in advance $36 for 10 days, and during 1934, $25, so that this material approximates that of a private ward, with no colored women, and a frequency of syphilis between 2 and 3%. The system is ideal for a small service which now averages 400 births yearly, since the deliveries are divided under a chief obstetrician between 2 continuous service associate obstetricians, with a 6-week intern supported by the chief resident physician. This management permits direct supervision by one of the staff of all operative deliveries other than outlet forceps, and all breeches and primiparas, leaving the instruction of the intern in episiotomy, outlet forceps and routine matters to the chief resident. Moreover, when the intern enters the service, he receives a condensed ward technique of 5 pages, a "code" of instructions, and has access to a large loose-leaf detailed technique book.

Causes of Maternal Deaths. 1, Pneumococcic cerebrospinal meningitis at 36 weeks gestation, contracted prior to Cesarian section performed during coma to protect the child, which survived; 2, hemorrhage and peritonitis following Cesarian section performed after 19½ hours' trial labor for contracted pelvis.

Comment. Again the forceps deliveries were mainly of the control type, and not too frequent. Cesarian sections were not too high,

and versions few. The morbidity standards, identical in all 3 institutions, namely fever of 100° F., twice consecutively in any 24-hour period excluding the first 24 hours after birth, the temperature taken every 4 hours, show fair results here.

The maternal mortality rate is excellent, but the fetal rate not so good, but again no exceptions or corrections of any sort. Analgesia in labor did not appear to account for asphyxia, about one-half of the mothers having received an average of phenobarbital sodium, gr. vi, with either morphin sulphate, gr. $\frac{1}{6}$, or codein sulphate, gr. $\frac{3}{4}$, or scopolamin, gr. $\frac{1}{150}$, terminating in light ether.

The Preston Retreat.* This unique institution, privately endowed in 1837 for obstetric care only, offers free to indigent married women of good character, up to 2 weeks prenatal, and up to 4 weeks postnatal, hospitalization in a fine maternity hospital. We therefore secure good American stock, under unusual control both indoors and out.

This is one of a very few active maternity services where the chief obstetrician personally examines and estimates the obstetric capacity of each woman prior to birth; and where truly conservative obstetrics may be attained by utilizing an experienced day or night superintendent for normal births, excluding breech deliveries.

Since the results of my predecessor, Dr. Richard Norris, and acting chief physician, Dr. Calvin Hartman, were so outstanding, I elected to continue the same conservative policy, with the results given in the table, constituting a comparison of methods and attainments not available elsewhere.

Causes of Maternal Deaths. 1, Myocardial failure following Cesarian section; 2, cerebral abscess due to septic embolism—4 weeks after practically healed incisional infection; 3, postpartum hemorrhage following breech decomposition-extraction for placenta previa in a woman who had experienced three hemorrhages, refused to inform even her husband, and delayed entering the hospital for "fear of instrumental birth."

Comment. The figures speak for themselves, and are very creditable, showing a maternal mortality incidence nearly 5 times less than the gross rate for Philadelphia. One-third of the mothers received "standard" Gwathmey rectal ether analgesia in labor, some nitrous oxid at birth. The incidence of breech births is very high (especially in view of routine reasonable effort at one external version 4 to 6 weeks before term), but showed extraordinarily good results under conservatism, each breech birth being considered as "interference."

A possible criticism is that we are neglecting to train assistants in operative obstetrics, but we are compensating for this through the courtesy of one of our consultants, Prof. W. R. Nicholson, by instructing University of Pennsylvania graduate medical students,

who are allowed to assist with repairs and occasionally to use forceps. Furthermore, in addition to the prime consideration being the welfare of the patient, is the fact that contact with a truly conservative method of treatment in itself constitutes good training.

Personal Cases.* In contrast with the ultraconservative Preston Retreat figures, the author offers the results of a series of consecutive hospital private births beyond 28 weeks' gestation over a longer period of years.

Causes of Maternal Deaths (none preventable). 1, Hemorrhage and shock after section for full term abdominal pregnancy with the placenta attached partly to intestines; baby survived; 2, embolism on 22d day after recovery from Cesarian section and postoperative cholecystitis; 3, pneumonia, contracted prior to natural term birth.

Comment. The most significant feature of these private cases is the very small proportion of mid forceps (10%) contrasted with the outlet applications, which is explained by routine deep sedation-analgesia. The great majority of our private clinical charts show no deviation from the normal, indicating that *any elevation of temperature above 99° F. constitutes morbidity; and that primary breast engorgement does not induce fever,* even though early lactation probably by allergic reaction, and of course later inflammation may produce morbidity.

Our personal maternal mortality rate is particularly significant in view of the fact that all specialists register many women with known complications; in other words, meet with a much higher proportion of obstetric hazards than occur in the general run of pregnancies, or even in women's clinics. However, let us take inspiration from two New York City clinics, where, during 1934, in the Women's Hospital, not one of 814 registered confinements proved fatal to a mother; and in the Lying-in Hospital services where, during 1934, in 4317 live births *of all types* there were only 0.17% maternal deaths.

Conclusions. 1. In general, conservative ward obstetrics is safest for mother and child; but reasonable assistance by a trained specialist yields as good results with more relief.

2. Interns should be pre-instructed in proper methods of delivery and the importance of rigid adherence to technique, and must be supervised in every abnormal labor and in all operative deliveries.

3. A member of the major obstetric staff should be present at all operative deliveries other than outlet forceps, and at all breech deliveries.

4. No effort whatever should be made to interfere with natural birth for the purpose of exhibition to students, since demonstration forceps or other operative deliveries instituted only for instruction of students or interns have been found unjustifiable.

OBSERVATIONS ON THE ETIOLOGY OF THE TOXEMIAS OF PREGNANCY.

THE RELATIONSHIP OF NUTRITIONAL DEFICIENCY, HYPOPROTEINEMIA, AND ELEVATED VENOUS PRESSURE TO WATER RETENTION IN PREGNANCY.* †

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APPROXIMATELY 25% of present-day maternal mortality is due to toxemia of pregnancy. Although such disorders as the anemias and polyneuritis of pregnancy have been included under this designation, these conditions may now be considered due to nutritional deficiency.[1–5] The term toxemia of pregnancy, as employed in this paper, designates the occurrence of arterial hypertension, with or without other abnormalities, during the latter months of pregnancy, in women known to have had normal blood pressures and no albuminuria early in gestation. The term eclampsia is reserved to designate the occurrence of convulsions and coma during the latter months of pregnancy, in labor, or during the puerperium, in women not presenting evidence of epilepsy, brain tumor or other adequate cause for the condition. Many observers believe that such events are the result of the action of one or more hypothetic toxins elaborated by the maternal or fetal organism. Although albuminuria is a common concomitant of toxemia, hypertension alone occurred in 585 of the 1036 cases of toxemia reported by Tillman and Watson.[6]

When convulsions and coma occur in the latter part of pregnancy or the puerperium, albuminuria and hypertension are usually present. However, convulsions and coma, considered to be eclampsia, have been reported without albuminuria by numerous clinicians,[7–10] and more rarely, have been observed in the absence of arterial hypertension.[10–11]

There remains, however, one other condition which is an exceedingly common concomitant of any and all of these other manifestations of toxemia, that is edema. In fact, most observers believe that either gross or occult edema is the *sine qua non* for the diagnosis of true toxemia of pregnancy. However, Fink[12] claims that 95% of all pregnant women have some degree of occult or gross edema.

* This work was made possible through the coöperation of the visiting surgeons and house staff of the Obstetrical Service of the Boston City Hospital, to whom the writer acknowledges his indebtedness.

† This paper was presented before the American Society for Clinical Investigation at Atlantic City, N. J., May 6, 1935.

More than 60 years ago, Rosenstein[13] advanced the thesis that cerebral edema was the cause of eclampsia. This he regarded as due to the effusion of serum from the "too-watery" blood into the cerebral tissues. Charpentier,[8] 13 years later, agreed with several compatriots that a diminished amount of albumin in the blood was a predisposing cause in the production of eclampsia.

More recently Wieloch[14] has observed the universal occurrence of water retention in his cases of toxemia of pregnancy, and Zangemeister[15] has actually demonstrated edema of the brain by means of trephining the skulls of eclamptic patients. Prutz,[16] and Arnold and Fay,[17] among many others, have made similar observations postmortem. Bingham[18] showed that toxemia developed only in those women who gained weight excessively. Although the cause of this weight gain was not determined, water retention might be its explanation. The cause of the marked water retention, which by general consensus of opinion[19] is so uniformly present in toxemia, has been variously ascribed to an excess production of pituitary antidiuretic hormone,[20] to primary kidney disease,[21] to a disturbance in the stability of the plasma colloids,[22] and to pressure of the enlarged uterus on the ureters,[23] among many other hypothetic causes. However, no satisfactory evidence has been presented for any of these theories. No modern investigator has reëxamined the hypothesis of Rosenstein, Prodhomme and others in the light of present-day knowledge concerning the mechanism of edema formation. Our understanding of this mechanism begins particularly with Starling's[24] demonstration of the rôle which the colloid osmotic pressure of the plasma proteins plays in counter-balancing the mechanical effect of the intra-capillary blood pressure. From Peters and Van Slyke's[25] excellent summary we learn that three main factors are involved: the intra-capillary blood pressure, the osmotic pressure of the plasma proteins, and the capillary permeability. In addition, edema apparently may occur as a result of the lack of certain still unknown accessory food factors (Yang and Huang,[26] Youmans,[27] Elsom[28] and others). Furthermore, Weech *et al.*[29] have recently shown that edema is formed in poorly nourished dogs at a much higher level of plasma proteins than in well-nourished dogs whose plasma proteins have been depleted by plasmapheresis. It is also apparent that edema cannot be formed unless there be supplied to the organism the necessary materials, that is, water and salt.

It is pertinent to consider at this point what changes occur in these various factors involved in water exchange during normal pregnancy. Grzechowiak[30] and Mufson[31] have directly measured the intracapillary pressure in pregnancy. Although it is not elevated in normal pregnancy, they found it to be markedly so in eclampsia and many cases of toxemia. However, the work of Landis and Gibbon[32] has so clearly demonstrated that the filtration of fluids out of the capillaries is directly proportional to the venous

pressure that studies of the latter in pregnancy by Runge[33] are important. The maximum venous pressures which he observed in normal non-pregnant subjects were 6.6 cm. and 7.2 cm. of water in the arm and leg respectively, contrasted to 8.9 cm. and 8.8 cm. respectively in normal women during the first 7 months of pregnancy and 9.8 cm. and 31.4 cm. respectively in normal women in the last 2 months of pregnancy. Barath and Weiner[34] found venous pressures of from 10 to 18 cm. of water in the arm at the end of normal pregnancy. It is thus apparent that normal pregnancy, particularly in the later months, may result in a distinct elevation of the venous pressure. If this is due to the mechanical effect of the enlarged uterus, one might expect it to be most marked in primiparæ with taut abdominal walls, in the obese, in the pyknic type, and in women with very large uteri from twin pregnancy or hydramnios. There is no doubt but that there is a higher incidence of toxemia in such individuals.[35,36,37] It is also apparent that the venous pressure is tremendously raised during the active stage of labor, during which time contractions of the abdominal musculature and diaphragm result in expulsive efforts.[38] It may be significant that 53% of all reported cases of eclampsia summarized from every available source[39] occurred during labor and 21% shortly after delivery. Unless a mechanical effect is involved, it is difficult to understand why three-fourths of all cases of eclampsia should occur during this relatively short period of the gravid state.

The concentration of the plasma proteins has been regularly found lowered during pregnancy.[22,41–44] This is corroborated by the data to follow. Eufinger,[22] Plass,[43] Eastman[44] and others have found this lowering of the plasma protein concentration most marked in toxemias of pregnancy and particularly in eclampsia, which is also evident from the data in this paper. The albumin fraction which has 4 times the osmotic pressure of the globulin fraction is particularly reduced. Although the degree of reduction of the osmotic pressure of the plasma proteins in pregnancy is ordinarily not below the so-called critical level for edema formation in the normal individual, it should be remembered that, in the presence of a second disturbance affecting filtration, there may be a much higher critical level, as has recently been shown in heart disease by Thomson.[45]

The cause of the lowering of the plasma protein concentration in pregnancy has not been clearly defined. One cause is apparent. It is recognized that the fetus draws upon the maternal organism for dietary factors, including its protein precursors, no matter what depletion of the mother results.[1] Therefore, if the mother's protein intake has been barely sufficient for her own economy and no change is made in her diet after pregnancy occurs, depletion of the mother's protein, especially in the last trimester of pregnancy, may be inevitable.

Disturbed gastro-intestinal function can condition dietary deficiencies. Such disturbances are common in pregnancy[2,46,47] and could play a rôle in conditioning protein deficiency in certain pregnant women in spite of an apparently adequate diet. Definite evidence on this point is, however, lacking. The part played in pregnancy by a failure to manufacture proteins through a disturbance of the organs involved in their production is entirely hypothetical but possibly important.

Observations. *The Plasma Proteins in Normal Pregnancy and in Toxemia.* The concentration of the total plasma protein and of the plasma albumin was determined by a modification of the method of Howe[48] on oxalated venous blood drawn without stasis, after the subject had been recumbent for at least 15 minutes. These observations were made on blood from the antecubital veins of 65 pregnant women. Of these 35 were normal and in the last 2 months of pregnancy, 20 were suffering from toxemia during a similar period of pregnancy, and 10 had eclampsia. The 20 with toxemia were known to have had normal arterial blood pressures and no albuminuria early in pregnancy, although at least 3 had had toxemia in preceding pregnancies, 1 having had eclampsia twice. At the time that blood was withdrawn for these determinations, each of the 20 patients with non-convulsive toxemia had a blood pressure of 150 (systolic) and 100 (diastolic) or higher. Seven had from 0.2 to 2 gm. of albumin per liter of urine (Tsuchiya method). The remaining 13 had only very slight traces of albumin in the urine. Only 3 had gross edema.

Each of the 35 normal pregnant women was closely questioned as to her usual protein intake both during and prior to pregnancy. Before any chemical analysis was made of the plasma, each dietary history was evaluated as either average or low in protein content. Of these women 20 had had diets containing moderate amounts of protein (estimated at 60 to 100 gm. per day), and 15 had had definitely low protein diets (estimated at less than 60 gm. per day). The failure to encounter any women with high protein intakes can probably be explained by the fact that they were all clinic patients and hence unable to afford the more costly protein foods in large amounts.

In Chart I are presented the plasma albumin concentrations of the 65 women grouped according to the condition which they presented.

It is apparent that in toxemia, with or without convulsions, the plasma albumin concentration is decidedly lower than in normal pregnant women. The average concentration of the plasma albumin in the 10 patients with eclampsia was 2.6%, in the 20 patients with toxemia without convulsions 3.1% and in the 35 normal pregnant women 3.56%. The lowering of the plasma albumin concentration in the 20 patients with non-convulsive toxemia can hardly be

ascribed to a loss of albumin in the urine, as 13 of these women had only very slight albuminuria. The average concentration of plasma albumin was lower in the normal subjects with poor protein intakes than in those with average intakes.

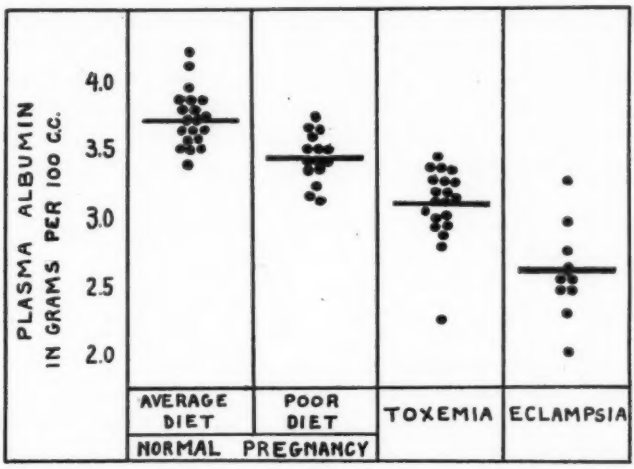

CHART I.—Plasma albumin concentration during the last 2 months of gestation in 20 normal women on average protein diets, in 15 normal women with low-protein intakes, in 20 women with non-convulsive toxemia of pregnancy, and in 10 with eclampsia. Each dot represents 1 patient. The horizontal lines represent the average values for each group.

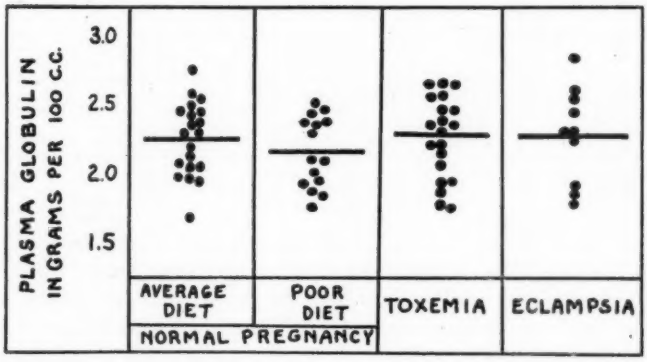

CHART II.—Plasma globulin concentration in the same group as in Chart I.

In Chart II the data on plasma globulin concentration obtained on the same 65 women is shown. The entire absence of correlation between diet, toxemia or eclampsia and the level of globulin is obvious.

Because, however, it is the colloid osmotic pressure exerted by both the albumin and globulin that is of importance with regard to

edema formation, the osmotic pressure of both fractions together has been calculated by Wells, Youmans and Miller's method[49] in each case (Chart III). The average osmotic pressure was lowest in eclampsia (175 mm. of water), next in non-convulsive toxemia (215 mm.), next in normal pregnant women with poor diets (232 mm.), and highest in those with good diets (258 mm.).

The Venous Pressure in Normal Pregnancy and in Toxemia. The venous pressure of 20 pregnant women during the last trimester of pregnancy, whose arterial blood pressures were 150 mm. Hg systolic and 100 mm. Hg diastolic or higher, and of 20 normal pregnant women during the last 2 months of gestation was determined by

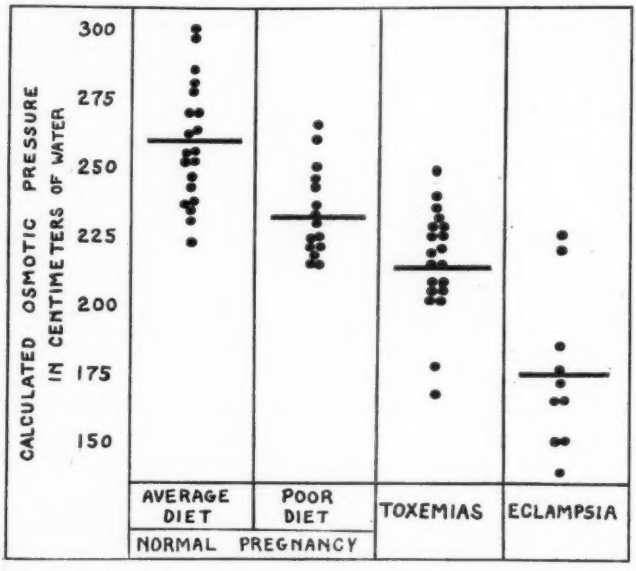

CHART III.—Calculated osmotic pressure of the total plasma proteins in the same group as in Chart I.

the method of Moritz and Tabora.[50] Readings were made after the subjects had been in a recumbent position for at least 15 minutes. The average venous pressure of normal non-pregnant individuals has been given by Eyster[51] as 5 cm. of water, with a maximum of 11 cm. During the last 2 months of normal pregnancy (Chart IV) the average venous pressure of 20 women was 10 cm. of water with a maximum of 18 cm. The average venous pressure of the 20 patients with toxemia was 13.3 cm. of water, a value not significantly different from normal pregnant women but distinctly higher than in normal non-pregnant subjects.

The impression obtained was that the venous pressure was particularly elevated in the short, stocky, obese women and in the

extremely thin and rather frail appearing women whose abdomens seemed hardly large enough to accommodate a full-term pregnant uterus.

Dietary Histories of Women with Toxemia of Pregnancy. The dietary histories of 20 pregnant women with toxemia, were carefully studied. Six of these women had had severe nausea and vomiting for several months early in pregnancy which had greatly limited their total intake, concentrated carbohydrates being their chief food during the period of emesis. Two other patients had had

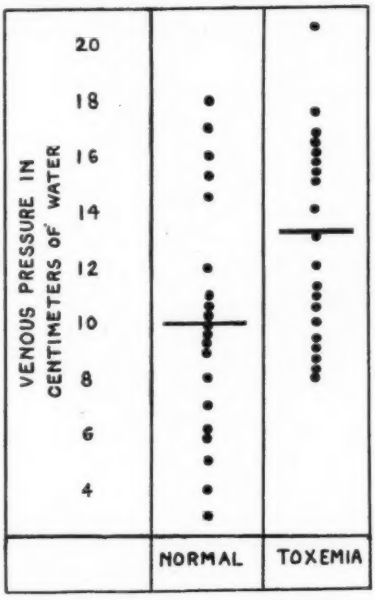

CHART IV.—Venous pressures in 20 normal pregnant women and in 20 with non-convulsive toxemia of pregnancy, all within the last 2 months of gestation. Dots and horizontal lines as before.

moderate emesis which had caused them to restrict their food to a certain extent. Of the 20 women, 18 had eaten little meat or other protein foods, not only during pregnancy but often over a period of years. The daily protein intake of these patients was estimated at less than 50 gm. daily. At least half of them stated that they were "poor meat eaters." Of the 20, 9 specified that they were very fond of and ate sweets and pastries in large amounts. Fifteen, who had accurate knowledge of their weight before pregnancy, had gained 20 to 44 pounds during gestation.

Results of Treatment of Toxemia of Pregnancy with a Special Diet High in Protein. Of the 20 pregnant women with toxemia, each of whom had an arterial blood pressure of 150 (systolic) and 100 (diastolic) or higher, 15 were given a diet containing 260 gm. of protein, 150 gm. of carbohydrate and 70 gm. of fat (2270 calories).

The protein was supplied in the form of lean meats, egg whites, skimmed milk and 300 gm. of raw liver pulp daily. Fluids were allowed freely. No purgation was employed. These patients were in the hospital during the period of observation but were not confined to bed. Ten of these 15 also received by daily intramuscular injections 5 cc. of a vitamin B_1 concentrate and 5 cc. of Solution Liver Extract—Lilly (N. N. R.).* The latter is believed to contain the pellagra and black-tongue preventative fraction of the vitamin B complex.

The weight changes of these 15 women at the end of a fortnight of this treatment are shown in Chart V. In general, weight was

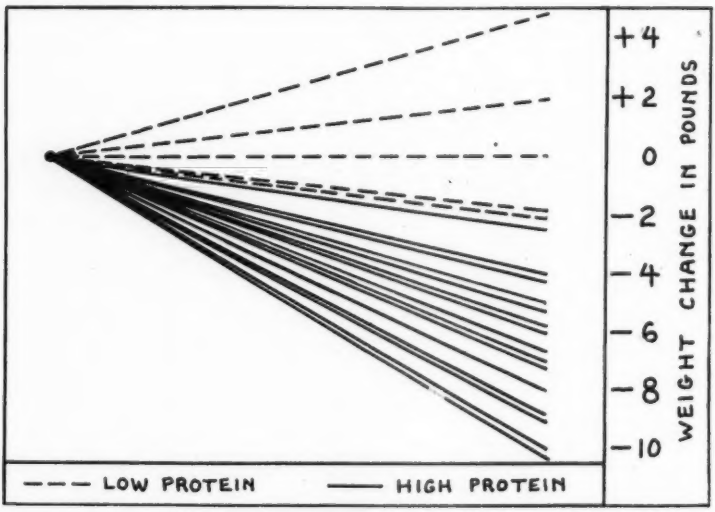

CHART V.—Weight changes after 2 weeks of 5 women with non-convulsive toxemia of pregnancy receiving a 20 gm. protein diet and of 15 similar women receiving a 260 gm. protein diet and parenteral injections of vitamin B.

lost steadily during this period in spite of the fact that they had daily about 2270 calories and were largely at rest. The amount of weight lost depended particularly on the proportional amount gained during the earlier months of pregnancy. In 3 patients gross edema completely disappeared, so that there was a marked loss in weight within 20 days. After the period of weight loss or within 3 weeks or less, the patients usually showed slow gains in weight consistent with the caloric intake. Rarely did the weight reach a level as high as that observed upon admission to the hospital. That this loss of weight during the first 2 or 3 weeks of treatment was due to the disappearance of either gross or occult edema seems to be very probable.

* Kindly supplied by Eli Lilly and Co., Indianapolis, Ind.

Coincident with the loss of weight, symptoms such as headache and visual disturbances were abated. In Chart VI, the arterial blood pressure of these women is shown at weekly intervals. In no case did the pressure rise after treatment was instituted. It is of interest that in every case the arterial blood pressure fell to below a systolic level of 140 mm. of mercury and to below a diastolic level of 90 mm. of mercury within 3 weeks of commencing treatment. The records indicate that the more acute the onset of the arterial

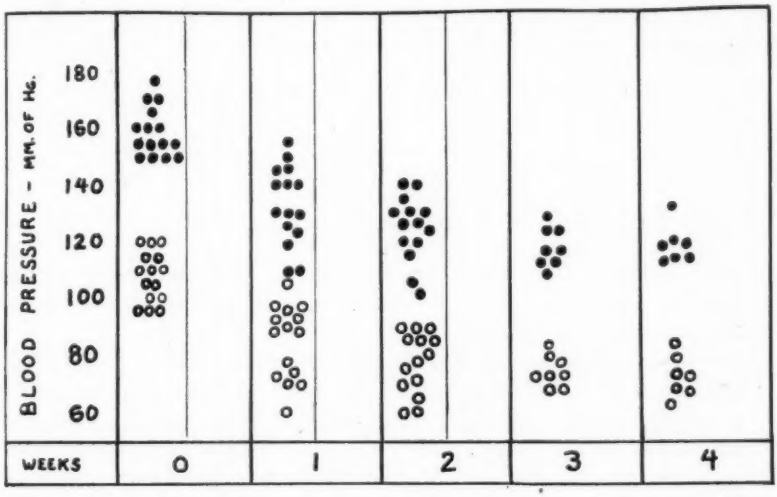

CHART VI.—Arterial blood pressures in successive weeks of 15 women with non-convulsive toxemia of pregnancy receiving a high-protein diet. The solid circles represent the systolic blood pressure, the open circles, the diastolic blood pressure. Seven of the patients were delivered by the end of the third week. No postpartum pressures are shown.

hypertension and the earlier the treatment, the more rapid was the response.

Albuminuria either remained unchanged or decreased in degree. No evidence suggesting that such a diet might lead to uremia can be drawn from Table 1, in which are presented the non-protein nitrogen values for these 15 women before and after the institution of the high-protein diet.

The calculated osmotic pressure of the plasma proteins in these women rose in 2 weeks an average of 7% of the initial level, usually by virtue of rises in both albumin and globulin fractions.

No fetal mortality occurred after the institution of this special diet.

After 3 of the above patients received the special diet in the hospital for 1 month, they returned to their homes, continuing the diet to the best of their abilities, during a period of 1 to 2 months

TABLE 1.—THE NON-PROTEIN NITROGEN OF THE BLOOD PLASMA IN 15 PATIENTS WITH NON-CONVULSIVE TOXEMIA OF PREGNANCY BEFORE AND AFTER ADMINISTRATION OF A HIGH-PROTEIN DIET.

Before mg. per 100 cc.	After mg. per 100 cc.
15	25
20	27
18	25
18	30
18	33
22	32
13	35
17	25
15	27
18	23
18	31
13	25
14	28
16	27
11	22
Average 16.4	Average 27.6

before each was delivered. In no instance was there any return of toxemic symptoms. Weight curves showed no evidence of recurrence of occult edema.

Results of Treatment of Toxemia of Pregnancy with a Low-protein Diet. Five of the 20 pregnant women with toxemia, with as nearly as possible identical signs and symptoms as the 15 women mentioned immediately above, were given a diet containing 20 gm. of protein, 65 gm. of fat and 400 gm. of carbohydrate. This diet contained 2265 calories or approximately the same number as the high-protein diet. However, it contained no meat, milk, fish, or eggs. The sodium chlorid content was essentially the same as that of the high-protein diet. The vitamin content was low. Fluids were allowed freely and no purgation was employed. The weights of these 5 women during a period of 2 weeks are shown in Chart V. One patient gained 5.25 pounds, a second 1.75 pounds, and the remaining 3 lost 0.25, 1.75 and 2 pounds each. The blood pressure (Chart VII) in 2 cases had fallen to normal within 2 weeks, in the remaining 3 patients it either rose or was stationary. Albuminuria was unchanged in 3 of the 5 patients, and increased from a faint trace to 0.3 and 15 gm. per liter respectively in the remaining 2 women. The calculated osmotic pressure of the plasma proteins fell an average of 9% of the initial value in these 5 women, the loss being chiefly at the expense of the albumin fraction.

Discussion. It is apparent that edema disease in pregnancy, mechanically complicated as it is by the large intraäbdominal mass of the pregnant uterus, an elevated venous pressure, and the constant drain on the protein reserves of the mother, must necessarily differ from edema disease in the non-pregnant individual. It is of

interest, however, that Yang and Huang[26] have recorded the occurrence of convulsions as well as arterial hypertension in the "wet" form of beriberi. Cowgill and his associates[52] have shown that the need for vitamin B increases with elevation of the metabolism. Since the basal metabolic rate is raised about 20% in pregnancy, considerably more vitamin B is probably required by pregnant women. Hence a deficiency of this factor may easily occur in pregnancy.

There is evidence to suggest that hemoglobin regeneration following the administration of iron is slower in pregnant than in nonpregnant patients with hypochromic anemia.[1] One would expect

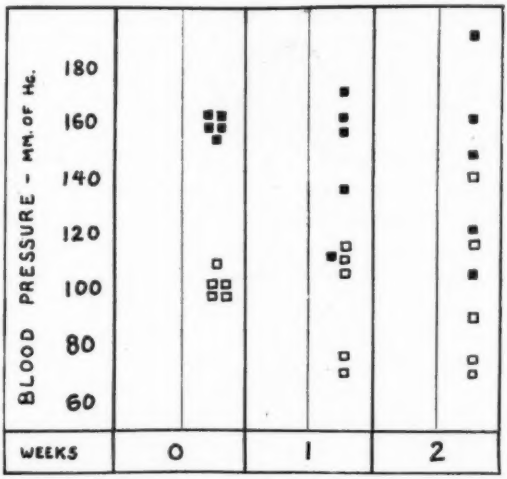

CHART VII.—Arterial blood pressures in successive weeks of 5 women with nonconvulsive toxemia of pregnancy receiving a low-protein diet. The solid squares represent the systolic blood pressure, the open squares, the diastolic blood pressure.

similarly that regeneration of plasma protein would be slower in pregnant women because of the constant demands of the fetus.

The weight changes of the 15 patients receiving the high-protein diet may be ascribed to any number of factors, such as rest in the hospital, or an increased nitrogen excretion resulting in diuresis. However, the failure of the control group to show changes of a similar magnitude suggests that the rest obtained is but a minor factor. Whether the patients who received the high-protein diet and injections benefited because of the protein content of the diet or because of receiving accessory food factors or both, cannot be determined at present.

The rôle of tissue resistance, lymph flow, and capillary permeability in edema formation in pregnancy has not been touched upon because of the paucity of our knowledge of these factors. The one

pertinent study[53] which has been made of edema fluid in toxemias of pregnancy has shown its protein content to be low, suggesting that there is no abnormal alteration of capillary permeability such as exists in certain other types of edema.

Because the arterial blood pressure is subject to spontaneous fluctuations both in normal and hypertensive subjects, and because rest frequently lowers both systolic and diastolic levels, no conclusions should be drawn from the fact that there was a lowering of the arterial blood pressure in each of the 15 women treated with the high-protein diet. It should be noted that this also occurred in 2 of the 5 patients receiving the low-protein diet.

The observations recorded in this paper fail to substantiate the prevalent belief that patients with toxemia of pregnancy should be treated by means of a restricted protein intake. It must be remembered, however, that none of these patients had either albuminuria or arterial hypertension during the first half of pregnancy. Approximately 5 of every 6 patients diagnosed as having toxemia of pregnancy in our pre-natal clinic were excluded from this study because there was no satisfactory evidence that the blood pressure was normal and the urine free of albumin during the early months of pregnancy. It might be added that a few observations, not recorded here, fail to show that any harm results from the use of high-protein diets in pregnant women with pre-existing arterial hypertension or albuminuria, or does such a diet appear to have any beneficial effect on such women.

Summary. 1. In 20 cases of non-convulsive toxemia of pregnancy the average osmotic pressure of the plasma proteins was 215 mm. of water, in 10 cases of eclampsia it was 175 mm. of water and in 20 normal pregnant women with adequate diets it was 258 mm. of water. In 15 normal pregnant women who had partaken of diets low in protein the average osmotic pressure of the plasma proteins was 232 mm. of water.

2. The average venous pressure in 20 normal pregnant women during the last 2 months of pregnancy was 10 cm. of water (range 3 to 18 cm.) and in 20 patients with non-convulsive toxemia of pregnancy 13.3 cm. (range 8 to 20.5 cm.), values which are at least twice as high as average figures for normal non-pregnant subjects.

3. The dietary histories of 20 toxemic pregnant women showed a low-protein intake, probably less than 50 gm. per day, frequently over a period of years.

4. Fifteen women suffering from toxemia of pregnancy were treated by means of a diet containing 260 gm. of protein, 150 gm. of carbohydrate and 70 gm. of fat. Ten also received parenteral injections of a vitamin B_1, concentrate and Solution Liver Extract—Lilly (N.N.R.), the latter because of its content of the pellagra-preventative portion of the vitamin B complex. Each of the 15 women showed a loss of weight readily attributable to decrease of

occult or gross edema, together with a gradual disappearance of the signs and symptoms of toxemia. No fetal mortality occurred after treatment had been instituted.

5. Five similar pregnant women suffering from toxemia were treated by means of a diet of approximately equal caloric value containing 20 gm. of protein, 400 gm. of carbohydrate, and 65 gm. of fat. No significant loss of gross or occult edema occurred. Two of the patients became decidedly worse during a period of 2 weeks.

6. It is believed that a manifestation of toxemia of pregnancy is water retention. This water retention probably occurs as a result, among other factors, of a lowered osmotic pressure of the plasma proteins, usually in the presence of an increased venous pressure. The results recorded in this paper suggest that a restricted dietary intake of protein in pregnancy is harmful, and that no injurious consequences follow the administration of high-protein diets to women with toxemia of pregnancy. The beneficial results observed in these patients may well have been due to the large protein intake and to the parenteral administration of accessory nutritional factors.

The writer is indebted to Miss Margaret Adams and Dr. F. H. L. Taylor for carrying out the chemical determinations reported in this paper.

REFERENCES.

1. Strauss, M. B., and Castle, W. B.: Am. J. Med. Sci., **185**, 539, 1933.
2. Davies, D. T., and Shelley, U.: Lancet, **2**, 1094, 1934.
3. Strauss, M. B., and McDonald, W. J.: J. Am. Med. Assn., **100**, 1320, 1933.
4. Fouts, P. J., Gustafson, G. W., and Zerfas, L. G.: Am. J. Obstet. and Gynec., **28**, 902, 1934.
5. Gerstle, M., Jr., and Lucia, S. P.: Calif. and Western Med., **40**, 167, 1934.
6. Tillman, A. J. B., and Watson, B. P.: Am. J. Obst. and Gynec., **29**, 19, 1935.
7. Schroder, quoted by Ingerslev.[9]
8. Charpentier, A.: A Practical Treatise on Obstetrics, New York, William Wood & Co., vol. **2**, 1887.
9. Ingerslev, E.: Ztschr. f. Geburtsh u. Gynäk., **6**, 171, 1881.
10. Theobald, G. W.: J. Obst. and Gynec. Brit. Emp., **36**, 1, 1929.
11. Strauss, M. B.: Unpublished observations.
12. Fink, K.: Ztschr. f. Geburtsh. u. Gynäk., **84**, 1, 1921.
13. Rosenstein, S.: Traité Pratique des Maladies des Reins, traduit de l'Allemand sur la deuxiene edition, Paris, Adrien Delahaye, 1874.
14. Wieloch, J.: Arch. f. Gynäk., **123**, 337, 1925.
15. Zangemeister, W.: Deutsch. med. Wchnschr., **37**, 1879, 1911.
16. Prutz, W.: Ztschr. f. Geburtsh. u. Gynäk., **23**, 1, 1892.
17. Arnold, J. O., and Fay, T.: Surg., Gynec. and Obst., **55**, 129, 1932.
18. Bingham, A. W.: Am. J. Obst. and Gynec., **23**, 88, 1932.
19. Stander, H. J.: Medicine, **8**, 1, 1929.
20. Anselmino, K. J., and Hoffman, F.: Arch. f. Gynäk., **147**, 652, 1931.
21. FitzGibbon, G.: J. Obst. and Gynec. Brit. Emp., **29**, 402, 1922.
22. Eufinger, H.: Klin. Wchnschr., **7**, 492, 1928.
23. Poten, W.: Monatschr. f. Geburtsh. u. Gynäk., **69**, 25, 1925.
24. Starling, E. H.: J. Physiol., **19**, 312, 1895–1896.
25. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Vol. **1**, Interpretations, Baltimore, The Williams & Wilkins Company, 1932.
26. Yang, C. S., and Huang, K. K.: Chinese Med. J., **48**, 20, 1934.
27. Youmans, J. B.: J. Am. Med. Assn., **99**, 883, 1932.
28. Elsom, K. O'S.: J. Clin. Invest., **14**, 40, 1935.
29. Weech, A. A., Snelling, C. E., and Gœttsch, E.: Ibid., **12**, 193, 1933.

30. Grzechowiak, F.: Ztschr. f. Geburtsh. u. Gynäk., **87**, 128, 1924.
31. Mufson, I.: Am. J. Obst. and Gynec., **15**, 800, 1923.
32. Landis, E. M., and Gibbon, J. H.: J. Clin. Invest., **12**, 105, 1933.
33. Runge, H.: Arch. f. Gynäk., **122**, 142, 1924.
34. Barath, E., and Weiner, P.: Ztschr. f. Klin. Med., **125**, 243, 1933.
35. Hinselmann, H.: Die Eklampsie, Bonn, F. Cohen, 1924.
36. McIlroy, L.: Lancet, **2**, 291, 1934.
37. Williams, J. W.: Obstetrics, Ed. V., New York, D. Appleton & Co., 1925.
38. Lloyd, J. J., and Richard, E. K.: Am. J. Med. Sci., **189**, 119, 1935.
39. Hinselmann, H., Nettekoven, H., and Silberbach, W.: Arch. f. Gynäk., **116**, 443, 1923.
40. Zangemeister, W.: Ztschr. f. Geburtsh. u. Gynäk., **49**, 92, 1903.
41. Mahnert, A.: Arch. f. Gynäk., **114**, 168, 1921.
42. Dieckmann, W. J., and Wegner, C. R.: Arch. Int. Med., **53**, 353, 1934.
43. Plass, E. D., and Bogert, L. J.: Bull. Johns Hopkins Hosp., **35**, 361, 1924.
44. Eastman, N. J.: Am. J. Obst. and Gynec., **20**, 343, 1930.
45. Thomson, W. A. R.: Quart. J. Med., **3**, 587, 1934.
46. Arzt, F.: Am. J. Obst. and Gynec., **20**, 382, 1930.
47. Strauss, M. B., and Castle, W. B.: Am. J. Med. Sci., **184**, 655, 1932.
48. Howe, P. E.: J. Biol. Chem., **49**, 109, 1921.
49. Wells, H. S., Youmans, J. B., and Miller, D. G., Jr.: J. Clin. Invest., **12**, 1103, 1933.
50. Moritz, F., and v. Tabora, D.: Deutsch. Arch. f. Klin. Med., **98**, 475, 1910.
51. Eyster, J. A. E.: Clinical Aspects of Venous Pressure, New York, The Macmillan Company, 1929.
52. Cowgill, G. R.: The Vitamin B Requirement of Man, New Haven, Yale University Press, 1934.
53. Hellmuth, K.: Zentralbl. f. Gynäk., **46**, 290, 1922.

(Titles have been omitted for sake of brevity).

ERYTHEMA ANNULARE RHEUMATICUM.

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In 1922 Lehndorff and Leiner,[1] under the title "Erythema Annulare" published an account of a typical exanthem occurring during the course of rheumatic endocarditis. Lehndorff,[2] in 1930, again described "Erythema Annulare Rheumaticum" and emphasized the fact that it occurs only in rheumatic children with endocardial involvement. While making the rounds at the Mautner-Markhof Kinderspital in Vienna in 1925, the late Professor Leiner demonstrated this rash to me in a child with rheumatic endocarditis. Since then I have had the opportunity of following a group of children suffering with rheumatic endocarditis at the Spaulding School for Crippled Children, and during the course of my examinations I have noted this distinctive rash in 6 children. The following cases may be cited:

Case Abstracts. CASE 1.—T. J., a 14-year-old boy, had frequent attacks of tonsillitis. After an attack of scarlet fever at the age of 7 years, he developed an arthritis which was followed by mitral endocarditis. Two sisters have had rheumatic fever and rheumatic endocarditis. At the time of examination for admission to the Spaulding School, November 6, 1931, it was stated that he had had frequent attacks of epistaxis for a year, and that the eruption appeared frequently on his chest, abdomen and back, especially when he did not feel well. The patient had been followed at the Illinois Research Hospital by Dr. Gustav Weinfeld and was referred by by him to the Spaulding School. The child was fairly well developed, skin was somewhat pale, tonsils had been removed, throat was clear, heart showed moderate enlargement to the left, there was no diffusion of the apex, and no precordial bulge. There was no thrill. A presystolic, systolic murmur, best heard at the apex, was transmitted to the axilla and to the base. Pulmonary second sound was accentuated, and the aortic second sound was clear. There was no clubbing of the finger nails. An annular erythema, consisting of narrow rings 1 to 1.5 cm. in diameter, of a pale pink color, was noted on the chest, abdomen, and to some extent on the back. The rash was of a macular character and the skin was free from edema, hemorrhage, or itching. The patient was unaware of the rash, except when he looked at his skin and noted its occurrence. On questioning the mother and the boy, the fact was brought out that whenever he did not feel up to standard or had a cold with fever, the rash occurred more prominently and lasted for some days. On Roentgen ray examination, a teleoroentgenogram at 6 feet distance revealed a moderate enlargement to the left with a mitral contour of the left heart border. The electrocardiogram showed a rate of 96 with a *P–R* complex of 0.16 seconds. There was a sinus rhythm with a slurring of the *Q–R–S* complex in I, II and III. *T* III was isoelectric. There was a left axis deviation. The systolic blood pressure was 128, diastolic 70. The red blood count was 6.1 million, hemoglobin (Tallqvist) was 85%; white blood cells, 7550.

Progress at School. The boy has attended school fairly regularly and has been well with the exception of occasional upper respiratory infection. At times when he has a slight temperature elevation or a cold the school nurse reports that the annular erythema noted at the first examination reappears on his chest and abdomen. (Fig. 1.)

CASE 2.—J. D., aged 14, was referred from the Municipal Tuberculosis Dispensary, and examined for admission to the Spaulding School January 3, 1933. At 10 the patient had an attack of acute rheumatic fever with elevation of temperature and swollen and painful joints of the shoulders, hands, knees and ankles. Subsequent to this attack the child was examined by a physician and the mother was told that he had heart disease. A similar attack of rheumatic fever was experienced in October, 1932, though of a shorter duration. The child had had frequent attacks of tonsillitis. though there was no history of any contagious disease. Two siblings were living and well. The patient was a thin, poorly nourished boy, and rather pale. There was no cyanosis. The throat was clear, the tonsils hypertrophied and cryptic. The heart was markedly enlarged downward to the left. The apex beat was diffuse in the fifth and sixth left interspaces outside of the midclavicular line. The precordium was bulging and there was a definite heave at the back systole. There was no thrill. There was a presystolic, systolic murmur at the apex transmitted to the axilla, and a diastolic murmur over the aortic area transmitted to the third interspace to the left of the sternum. The second pulmonic sound was poorly transmitted. The heart rhythm was regular, and a Corrigan pulse was noted. At the time of the examination the child had a definite nasopharyngitis, with a temperature of 99.6° F. An annular erythema of bluish-pink color and macular

30. Grzechowiak, F.: Ztschr. f. Geburtsh. u. Gynäk., **87**, 128, 1924.
31. Mufson, I.: Am. J. Obst. and Gynec., **15**, 800, 1923.
32. Landis, E. M., and Gibbon, J. H.: J. Clin. Invest., **12**, 105, 1933.
33. Runge, H.: Arch. f. Gynäk., **122**, 142, 1924.
34. Barath, E., and Weiner, P.: Ztschr. f. Klin. Med., **125**, 243, 1933.
35. Hinselmann, H.: Die Eklampsie, Bonn, F. Cohen, 1924.
36. McIlroy, L.: Lancet, **2**, 291, 1934.
37. Williams, J. W.: Obstetrics, Ed. V., New York, D. Appleton & Co., 1925.
38. Lloyd, J. J., and Richard, E. K.: Am. J. Med. Sci., **189**, 119, 1935.
39. Hinselmann, H., Nettekoven, H., and Silberbach, W.: Arch. f. Gynäk., **116**, 443, 1923.
40. Zangemeister, W.: Ztschr. f. Geburtsh. u. Gynäk., **49**, 92, 1903.
41. Mahnert, A.: Arch. f. Gynäk., **114**, 168, 1921.
42. Dieckmann, W. J., and Wegner, C. R.: Arch. Int. Med., **53**, 353, 1934.
43. Plass, E. D., and Bogert, L. J.: Bull. Johns Hopkins Hosp., **35**, 361, 1924.
44. Eastman, N. J.: Am. J. Obst. and Gynec., **20**, 343, 1930.
45. Thomson, W. A. R.: Quart. J. Med., **3**, 587, 1934.
46. Arzt, F.: Am. J. Obst. and Gynec., **20**, 382, 1930.
47. Strauss, M. B., and Castle, W. B.: Am. J. Med. Sci., **184**, 655, 1932.
48. Howe, P. E.: J. Biol. Chem., **49**, 109, 1921.
49. Wells, H. S., Youmans, J. B., and Miller, D. G., Jr.: J. Clin. Invest., **12**, 1103, 1933.
50. Moritz, F., and v. Tabora, D.: Deutsch. Arch. f. Klin. Med., **98**, 475, 1910.
51. Eyster, J. A. E.: Clinical Aspects of Venous Pressure, New York, The Macmillan Company, 1929.
52. Cowgill, G. R.: The Vitamin B Requirement of Man, New Haven, Yale University Press, 1934.
53. Hellmuth, K.: Zentralbl. f. Gynäk., **46**, 290, 1922.

(Titles have been omitted for sake of brevity).

ERYTHEMA ANNULARE RHEUMATICUM.

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In 1922 Lehndorff and Leiner,[1] under the title "Erythema Annulare" published an account of a typical exanthem occurring during the course of rheumatic endocarditis. Lehndorff,[2] in 1930, again described "Erythema Annulare Rheumaticum" and emphasized the fact that it occurs only in rheumatic children with endocardial involvement. While making the rounds at the Mautner-Markhof Kinderspital in Vienna in 1925, the late Professor Leiner demonstrated this rash to me in a child with rheumatic endocarditis. Since then I have had the opportunity of following a group of children suffering with rheumatic endocarditis at the Spaulding School for Crippled Children, and during the course of my examinations I have noted this distinctive rash in 6 children. The following cases may be cited:

Case Abstracts. CASE 1.—T. J., a 14-year-old boy, had frequent attacks of tonsillitis. After an attack of scarlet fever at the age of 7 years, he developed an arthritis which was followed by mitral endocarditis. Two sisters have had rheumatic fever and rheumatic endocarditis. At the time of examination for admission to the Spaulding School, November 6, 1931, it was stated that he had had frequent attacks of epistaxis for a year, and that the eruption appeared frequently on his chest, abdomen and back, especially when he did not feel well. The patient had been followed at the Illinois Research Hospital by Dr. Gustav Weinfeld and was referred by by him to the Spaulding School. The child was fairly well developed, skin was somewhat pale, tonsils had been removed, throat was clear, heart showed moderate enlargement to the left, there was no diffusion of the apex, and no precordial bulge. There was no thrill. A presystolic, systolic murmur, best heard at the apex, was transmitted to the axilla and to the base. Pulmonary second sound was accentuated, and the aortic second sound was clear. There was no clubbing of the finger nails. An annular erythema, consisting of narrow rings 1 to 1.5 cm. in diameter, of a pale pink color, was noted on the chest, abdomen, and to some extent on the back. The rash was of a macular character and the skin was free from edema, hemorrhage, or itching. The patient was unaware of the rash, except when he looked at his skin and noted its occurrence. On questioning the mother and the boy, the fact was brought out that whenever he did not feel up to standard or had a cold with fever, the rash occurred more prominently and lasted for some days. On Roentgen ray examination, a teleoroentgenogram at 6 feet distance revealed a moderate enlargement to the left with a mitral contour of the left heart border. The electrocardiogram showed a rate of 96 with a *P–R* complex of 0.16 seconds. There was a sinus rhythm with a slurring of the *Q–R–S* complex in I, II and III. *T* III was isoelectric. There was a left axis deviation. The systolic blood pressure was 128, diastolic 70. The red blood count was 6.1 million, hemoglobin (Tallqvist) was 85%; white blood cells, 7550.

Progress at School. The boy has attended school fairly regularly and has been well with the exception of occasional upper respiratory infection. At times when he has a slight temperature elevation or a cold the school nurse reports that the annular erythema noted at the first examination reappears on his chest and abdomen. (Fig. 1.)

CASE 2.—J. D., aged 14, was referred from the Municipal Tuberculosis Dispensary, and examined for admission to the Spaulding School January 3, 1933. At 10 the patient had an attack of acute rheumatic fever with elevation of temperature and swollen and painful joints of the shoulders, hands, knees and ankles. Subsequent to this attack the child was examined by a physician and the mother was told that he had heart disease. A similar attack of rheumatic fever was experienced in October, 1932, though of a shorter duration. The child had had frequent attacks of tonsillitis. though there was no history of any contagious disease. Two siblings were living and well. The patient was a thin, poorly nourished boy, and rather pale. There was no cyanosis. The throat was clear, the tonsils hypertrophied and cryptic. The heart was markedly enlarged downward to the left. The apex beat was diffuse in the fifth and sixth left interspaces outside of the midclavicular line. The precordium was bulging and there was a definite heave at the back systole. There was no thrill. There was a presystolic, systolic murmur at the apex transmitted to the axilla, and a diastolic murmur over the aortic area transmitted to the third interspace to the left of the sternum. The second pulmonic sound was poorly transmitted. The heart rhythm was regular, and a Corrigan pulse was noted. At the time of the examination the child had a definite nasopharyngitis, with a temperature of 99.6° F. An annular erythema of bluish-pink color and macular

in nature was noted over the lower abdomen from the level of the umbilicus to the symphysis pubis. The rash consisted of narrow rings about 1 cm. in diameter, some of which formed circles, others were serpentine or crescentic in form.

Progress. The boy attended school irregularly until the fall of 1933 when he was taken ill with another attack of rheumatic fever. Following this he developed a decompensated heart, was hospitalized for several months and died at home in February, 1934. Autopsy could not be obtained.

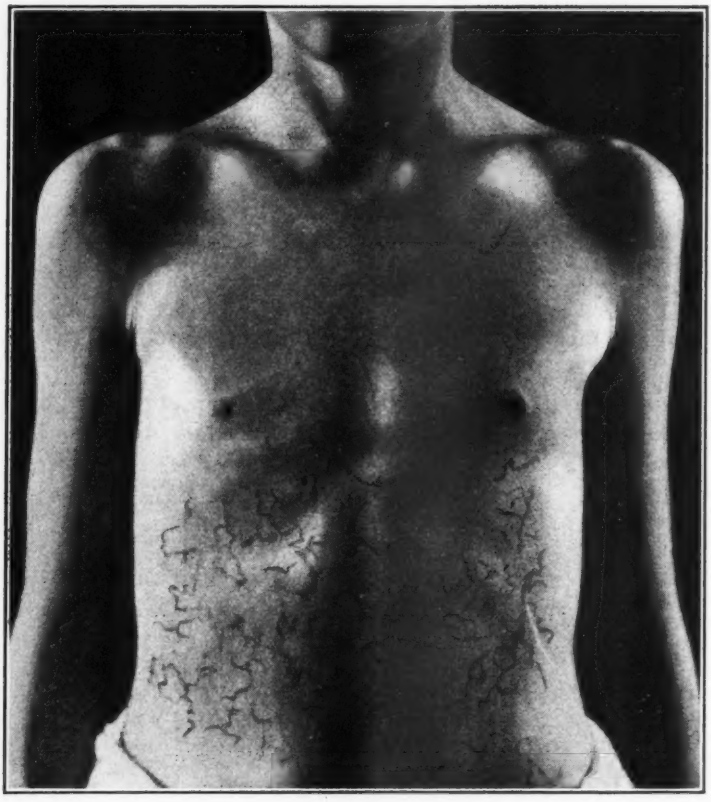

FIG. 1.—(Case 1.) Erythema annulare rheumaticum, as noted in a 14-year-old boy suffering with rheumatic endocarditis.

CASE 3.—M. H., a 12-year-old girl, was referred to the Spaulding School by the County doctor. She was examined on November 22, 1933, for admission. She had scarlet fever (1921), measles (1927), diphtheria and mumps (1929) and whooping cough (1930); also occasional attacks of tonsillitis. In December, 1930, she had an attack of rheumatic fever, at which time she was confined to bed for 2 weeks with fever and swollen joints. In April, 1931, she was seen at the Northwestern University Dispensary, complaining of joint pains. At this time she was sent to Wesley Hospital, where she was confined for 7 weeks. Two siblings are living and well. From time to time, the mother states, nodules have appeared on the

child's elbows, wrists and feet. Physical examination at the time of application for admission to the Spaulding School, showed a tall, thin, red-haired girl with a mitral facies. Her tonsils were rather large and cryptic. Her heart was somewhat enlarged to the left and the right border was at the sternal margin. The apex beat was diffuse, no thrill was noted. A presystolic, systolic murmur was heard at the apex and transmitted to the axilla. The aortic second sound was clear and the pulmonic second sound was markedly accentuated. Blood pressure was 134 systolic, 80 diastolic. There was no clubbing of the fingers and no rheumatic nodules were noted at the time of examination. At the time of this examination the skin was clear.

Progress at School. February 6, 1934, the child was reëxamined because she had been out of school for 1 week with a cold. At this time an annular erythema, consisting of a macular, pink rash was noted over her thorax, made up of rings from 1 to 2 cm. in diameter. The physical examination was essentially similar to that recorded above.

CASE 4.—E. S., was admitted to the Spaulding School on September 11, 1931, aged 11 years. He had measles, scarlet fever, and diphtheria in 1924, and had been confined to the City Contagious Diseases Hospital. In 1927, he had an attack of acute rheumatic fever, following which his tonsils had been removed. He was a rather thin boy of 11, throat clear, tonsils removed. His heart was moderately enlarged to the left, the rhythm was regular, there was a systolic, presystolic murmur at the apex, transmitted to the axilla. No thrill. The aortic second sound was clear, pulmonic second sound accentuated. Red blood cells, 4,950,000; hemoglobin, 85% (Tallqvist); white blood count, 7150. The Roentgen ray teleoroentgenogram showed moderately enlarged heart with a prominence in the left auricular region, suggesting the contour of a mitral lesion. The electrocardiogram showed a rate of 96, *P–R* interval 0.16 with normal rhythm; *Q–R–S* was slurred and widened in all leads; *T* I diphasic and a left axis deviation.

Progress. Attended school fairly regularly, though in February and March of 1933 he was confined to his home with an attack of acute rheumatism, at which time he had fever and swollen joints. On February 16, 1934 he was examined after an absence from school because of a cold. This examination was essentially the same as that on admission, with the exception that he was quite thin and pale. There was a diffusion of the apex beat, a marked bulging and heaving of the precordium. The rhythm was regular. Slight clubbing of the finger nails was noted. No rheumatic nodules. Over the skin of the chest and back there was a diffuse annular erythematous eruption, consisting of pink macular rings 1 to 2 cm. in diameter.

CASE 5.—R. N., admitted to the Spaulding School on March 8, 1935, aged 8, complained of shortness of breath on exertion. He had an attack of acute rheumatic fever in October, 1934, following which it was noted he had heart trouble. On physical examination it was noted that the patient was a small thin boy, rather pale, the heart rate was rapid and the apex slightly outside of the midclavicular line. Presystolic, systolic murmur at the apex transmitted to the axilla, second pulmonic sound accentuated. An annular erythematous rash was noted over the lower portion of the chest and the upper part of the abdomen. The lesions were circular and macular in nature. The rings were 1 to 1½ cm. in diameter, and the skin was free from edema or hemorrhage.

CASE 6.—C. J., a 14-year-old boy, complains of shortness of breath and fainting spells; admitted to the Spaulding School on March 8, 1935. In the past year he has had so-called growing pains. Tonsillectomy in 1929; scarlet fever in 1933, and pneumonia in January, 1935, at which time his heart trouble was discovered. Rather thin, small, pale boy. Apex beat is

diffuse. There is a slight precordial bulge with a heave, no thrill, heart is enlarged to the left, out and down, with slight enlargement to the right. Presystolic, systolic murmur at the apex which is transmitted to the axilla and to the base. Pulmonic second sound accentuated, the aortic second sound is normal. An annular erythematous rash is noted on the chest and abdomen and extends around the flanks and over the lower back. Small erythematous circles are also noted in the cubital spaces and along the flexor surfaces of the forearms. The rings are macular in nature and measure from 1 to 2 cm. in diameter. The mother states that she has noticed this rash when the boy felt poorly or had a cold.

Discussion. Since the publication of the description of erythema annulare rheumaticum by Lehndorff and Leiner (1922) it would seem of interest to examine the literature both before and after their description of this specific skin rash to note its observance by other authors. If we examine Cheadle's[3] classic monograph "The Various Manifestations of the Rheumatic State" (1889) we note as a frontispiece a colored print sketched from life, depicting a posterior view of the head and back of a child, showing large subcutaneous nodules on the occipital region of the head, along the spine, over the wings of the scapulæ and over the posterior iliac crests. Besides these nodules we note annular skin lesions which in the picture appear similar to erythema annulare rheumaticum, and which Cheadle terms erythema marginatum (Fig. 2). On page 46 of this treatise, he states: "The connection of erythema exudativum with the rheumatic state appears much more clearly in the case of children than of adults. With the latter it occurs occasionally; with children, according to my experience, it is common." According to Cheadle, the skin manifestations of rheumatic fever appear in various forms, either as erythema marginatum, as erythema papulatum, as erythema nodosum, or as urticaria. The erythema marginatum, according to Cheadle, is the most common type found. The following from Cheadle agrees with the precepts of Lehndorff and Leiner. "These varieties (speaking of the above named skin lesions) are not infrequently associated with endocarditis and pericarditis in the most serious cases."

Poynton and Paine[4] in their "Researches on Rheumatism" (1914), in discussing the cutaneous manifestations of rheumatic fever, note that "In the generalized cases the eruption is often multiform, and in some areas it may be by no means unlike a tinea circinata or erythema iris." They make no further note as to its association with endocarditis or the specificity of the lesion.

William Osler,[5] notes that in the erythema group of skin diseases cardiac symptoms rarely occurred and that acute endocarditis was a rare complication. Only 3 cases in Osler's series had heart murmurs, and he states that in none of his patients was it likely that endocarditis existed.

If we examine the more recent literature we note that Leichtentritt,[6] in 1930, recognizes the specific skin lesion, erythema annulare

rheumaticum, and substantiates the findings of Lehndorff and Leiner that it occurs in association with endocarditis. He points out that the occurrence of this lesion is an unfavorable prognostic sign. He feels that even though there be no apparent signs or symptoms, the occurrence of this lesion indicates the persistence of rheumatic infection.

Hans Rietschel,[7] includes a brief statement concerning erythema annulare rheumaticum and notes that the exanthem has been

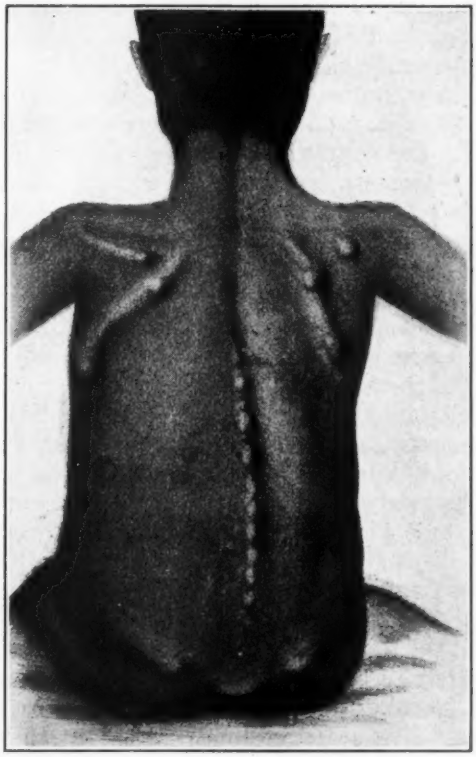

FIG. 2.—Reproduction of frontispiece from Cheadle's "The Various Manifestations of the Rheumatic State" 1889, showing annular rash associated with rheumatic endocarditis, which is termed "Erythema Marginatum."

observed only in endocarditis rheumatica and not in ulcerative endocarditis or subacute bacterial endocarditis.

Poynton and Schlesinger[8] (1931), devote very little space in their monograph to the subject of the skin manifestations in rheumatism. They make no mention of erythema annulare rheumaticum.

Wilfred Sheldon[9] notes the following: "*Erythema Marginatum.* This is a characteristic eruption of rheumatism. It appears as numerous slightly raised red streaks which are generally circular,

covering an area about as large as a shilling, or they may coalesce, and then have an irregular wavy outline. The rash occurs principally on the trunk, both back and front, and may also appear on the limbs. It does not itch. It comes out quickly within a few hours, and may be evanescent, or may persist for several days with constantly changing shape. It is likely to recur, and in the author's experience it has always been associated with evidence of cardiac rheumatism."

H. F. Swift[10] states: "The cutaneous manifestations of rheumatic fever consist of various exudative dermatoses, but none is absolutely typical of the disease, as similar rashes are seen in other infections and apparently as independent conditions. Various types of erythema multiforme are the most common; often the rash starts as flat papules, rapidly increasing in size, and clearing in the centers; finally the migratory borders of several lesions fuse into an extensive marginate erythema. Frequently the evolution and resolution occur within a few hours. Often such rashes recur for weeks or months. They commonly do not itch, hence may be easily overlooked. Occasionally purpura is seen."

Griffith and Mitchell[11] (1933) write: "Erythema of various sorts is prone to occur, and sometimes purpura, often associated with the arthritis. Purpura rheumatica, so-called, probably has no direct connection with rheumatism."

P. Bertoge[12] (1934) makes but a brief mention of erythema annulare rheumaticum, as described by Lehndorff and Leiner.

Ingerman and Wilson,[13] in 1924, reported that in 8% of their cases they observed erythema, urticaria and herpes zoster. "To what extent these were actually rheumatic manifestations or only associated conditions in rheumatic subjects, is difficult to determine."

In a recent article on the cutaneous lesions in rheumatic fever Chester and Schwartz[14] (1934) describe lesions mainly on the lateral surface of the legs and on the extensor surface of the forearms. They were rarely seen on the trunk. The lesion was described as consisting of maculopapular purpuric spots, which persisted from 1 to 6 months. The authors further state that the appearance of cutaneous lesions in children who have already had rheumatic fever should be regarded as a manifestation of reactivity. They report 9 cases in which these lesions were observed. In all their patients it is noted that a rheumatic endocarditis existed. Strangely enough, in their review of the cutaneous manifestations of rheumatic fever, they make no mention of the erythema annulare rheumaticum described by Lehndorff and Leiner. In a search through the various treatises on diseases of the skin in skin atlases, no reference can be found to this erythema.

Ormsby[15] states: "The term erythema annulare or circinatum is used to designate the lesions having a depressed center and an erythematous margin forming a ring. Occasionally these rings are arranged concentrically.

"When several rings coalesce by peripheral extension gyrate figures are formed and this is termed erythema figuratum. Erythema marginatum indicates a form in which a distinctly elevated and well defined marginal band is left as the sequel of the erythematous patch. Erythema papulatum or papulosum and erythema tuberculatum or tuberculosum refer to that type of the disorder in which the lesions are papular or nodular."

The various plates in Jacobi's[16] "Atlas of Dermochromes" under the heading of erythemas, have not the slightest similarity to erythema annulare rheumaticum.

Lehndorff[17] has included erythema annulare rheumaticum as a subhead under "Die Erythemkrankheiten des Kindesalters."

Summary. Erythema annulare rheumaticum (Lehndorff-Leiner) is a specific exanthem associated only with rheumatic endocarditis. The lesions are pale red or bluish-red, semicircles or rings which on first appearance may be from 2 to 4 mm. in diameter and which may develop into rings of 1 to 3 cm. in diameter. The lesions are found on the chest, over the abdomen, on the sides of the thorax, and on the back. They are rarely seen on the extremities and never on the face or mucous membranes. The lesions are never papular but always macular. There is no itching, edema or hemorrhage associated with them. They disappear without scaling or pigmentation.

Lehndorff estimates that erythema annulare rheumaticum occurs in about two-thirds of all cases of rheumatic endocarditis in children. Because of its transitory nature it is often overlooked. The rash is not associated with septic or ulcerative endocarditis or endocarditis lenta, and does not occur in other types of arthritis. It never occurs at the onset of an attack of acute rheumatic fever and only appears following the endocardial involvement. In fact, it so constantly indicates the persistence of a rheumatic infection in association with a cardiac involvement that it has been said rheumatic endocarditis may be diagnosed by merely seeing this rash on the skin. Its prognostic value, in my experience, is varied. In the 1 fatal case here reported it was an ominous sign. In the other 5 children the rash has been noted after illnesses varying from slight colds without febrile reaction, to recurrent attacks of rheumatism with fever.

In the group of children under my observation at the Spaulding School, I have noted this rash more frequently than I have been able to demonstrate subcutaneous nodules. The exact nature of the rash is as yet unknown. No one has as yet established a relationship between this rash and the tuberculin reaction, or the demonstration of tubercle bacilli by gastric lavage, as has been done in erythema nodosum.

Löwenstein and Reitter[18] have demonstrated a tuberculous bacillemia in cases of rheumatic endocarditis with erythema annulare

rheumaticum in Professor Knöpfelmacher's Clinic in Vienna. To date, this finding has not been definitely accepted as evidence of the tuberculous nature of rheumatic fever, and therefore, its significance with regard to rheumatism and the rash must be held in abeyance.

The only reported histologic examination of the skin in a case of erythema annulare rheumaticum, is the one of Carol and Van Krieken.[19] They excised a small area of skin from the abdomen of a 7-year-old girl who was sick with an acute rheumatic fever and an associated rheumatic endocarditis. The child showed the typical erythema annulare rheumaticum described by Lehndorff and Leiner, the rash being most marked upon the abdomen. The exanthem was present at intervals for 12 weeks. The sections of the skin from this case showed on histologic examination, an acute inflammatory process of the outer and intermediate portions of the cutis, consisting nearly entirely of an infiltration of neutrophils. The authors state that this finding differs histologically from the sections of skin examined in cases of urticaria, annulare and erythema exudativum multiforme Hebræ.

Finally it may be concluded that erythema annulare rheumaticum is exclusively associated with rheumatic endocarditis and its appearance has been noted only in association with such cases. The occurrence of this rash in children suffering with rheumatic endocarditis, as is the case with other cutaneous lesions found in this disease, may be considered as evidence of either the persistence of an active rheumatic endocarditis or as a sign of reactivation of the disease.

REFERENCES.

1. Lehndorff, H., and Leiner, C.: Annular Erythema. A Typical Exanthem in Endocarditis, Ztschr. f. Kinderh., **32**, 46, 1922.

2. Lehndorff, H.: Erythema Annulare Rheumaticum., Wien, Med. Wchnschr., **80**, 1449, 1930.

3. Cheadle, W. B.: The Various Manifestations of the Rheumatic State as Exemplified in Childhood and Early Life. Lectures Delivered before the Harveian Society, London, Smith Elder & Co., 1889.

4. Poynton, F. J., and Paine, A.: Researches on Rheumatism, New York, The Macmillan Company, p. 420, 1914.

5. Osler, W.: On the Visceral Manifestations of the Erythema Group of Skin Diseases, Am. J. Med. Sci., **127**, 1, 1904.

6. Leichtentritt, B.: Die rheumatische Infektion im Kindesalter, Ergebn. d. inn. Med. u. Kinderh., **37**, 62, 1930.

7. Rietschel, H.: "The Other Acute Infectious Exanthems and Erythemata" in Pfaundler and Schlossmann's Diseases of Children (English Translation, edited by M. G. Peterman), **3**, 231, Philadelphia, J. B. Lippincott Company, 1935.

8. Poynton, F. J., and Schlesinger, B.: Recent Advances in the Study of Rheumatism, Philadephia, P. Blakiston's Son & Co., 1931.

9. Sheldon, W.: "Rheumatism" in Thursfield and Paterson's Diseases of Children (First ed. edited by Garrod, Batten, and Thursfield), Baltimore, William Wood & Co., 1934, p. 1029.

10. Swift, H. F.: "Rheumatic Fever" in Cecil's A Textbook of Medicine, Philadelphia, W. B. Saunders Company, 1930, p. 87.

11. Griffith, J. P. C., and Mitchell, A. G.: The Diseases of Infants and Children, Philadelphia, W. B. Saunders & Co., 1933, p. 474.

12. Bertoge, P.: "Infectious Erythemas" in Nobécourt and Babonneix, Traité de Médecine des Enfants, **2**, 403, 1934, Paris, Masson et Cie.

13. Ingerman, E., and Wilson, M. G.: Rheumatism: Its Manifestations in Childhood Today, J. Am. Med. Assn., **82**, 759, 1924.
14. Chester, W., and Schwartz, S. P.: Cutaneous Lesions in Rheumatic Fever, Am. J. Dis. Child., **48**, 69, 1934.
15. Ormsby, O. X.: Diseases of the Skin, Philadelphia, Lea & Febiger, 1921, p. 127.
16. Jacobi's Atlas of Dermochromes, with entirely new and original text by Henry MacCormac, St. Louis, The C. V. Mosby Company, 1927.
17. Lehndorff, H.: "Die Erythemkrankheiten im Kindesalter" in Pfaundler and Schlossmann's Handbuch der Kinderheilkunde (10th volume, Die Hautkrankheiten des Kindesalters), Berlin, C. W. Vogel, 1935, p. 584.
18. Reitter, C., and Löwenstein, E.: Ueber den pathogenetischen Zusammenhang des akuten Gelenksrheumatismus mit der Tuberkelbazillämie, Wien, klin. Wchnschr., **45**, 293, 1932.
19. Carol, W. L. L., and van Krieken, J. A.: Zur Histopathologie der Erythema Annulare von Lehndorff and Leiner, Acta Pædiat., **17**, 372, 1935.

SUBCUTANEOUS FATTY NODES IN THE SACROILIAC AREA.

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Of a group of 170 unselected hospital patients, suffering from various complaints, subcutaneous nodes were palpated in the sacroiliac regions in 94 cases. In 45 of them the nodes were present unilaterally; in 49 others they were present bilaterally. The patients varied in age from 2 to 60 years. While the nodules were noted in thin persons, the incidence in stout women past middle age was generally highest. The nodes could be palpated over the sites of the sacroiliac joints; less often they were also present over or near the tips of the lumbar spinous processes (Fig. 1). The nature and character of these nodes were considered worthy of investigation. Since 33 of these patients had low back pains (muscular-skeletal in origin) a correlation was sought between the presence of the nodules and these pains. This was deemed especially appropriate since Stockman contends that inflammatory changes in the subcutaneous fat may be the cause of some of the symptoms referred to muscles or joints.[1] Of the 33 cases with low back pain, 16 had tender subcutaneous nodules in the sacroiliac area, while in 7 others the nodules were not tender.

In 4 cases the nodules were removed in order to ascertain their more intimate nature by gross and microscopic examination.

Case Reports. Case 1 (Admission No. D1038).—The patient was a woman, aged 50, who complained of severe pains in both lower loins of several months' duration. Occasionally the pains radiated down the posterior aspect of the right leg. Apart from the pain described, the history presented nothing remarkable. Clinical examination revealed tenderness over the right posterior inferior spine of the ilium (an anatomic landmark

for the location of the right sacroiliac joint). Forward bending of the trunk was slightly limited. No hamstring spasm was present in either lower extremity; neurologic examination was negative. Palpation of the sacroiliac regions revealed bilateral groups of subcutaneous nodules. Each side presented clumps of 6 to 8 nodes. They were freely movable under the skin and varied in size from a pea to an almond. The nodes were of the consistency of soft rubber. Those on the right side were very much more tender than those on the left. Roentgenogram of the pelvic bones showed arthritic changes in the sacroiliac joints. Over a period of 4 months the patient received diathermy, baking and local massage; improvement was negligible.

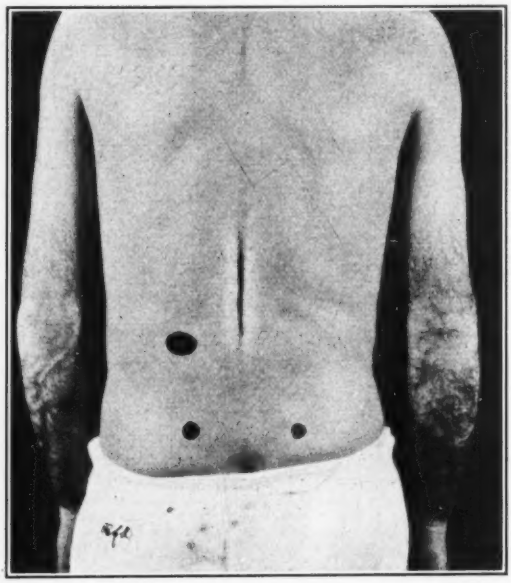

FIG. 1.—Note the location of the subcutaneous nodes.

Clinically the diagnoses considered were lipomas, neurolipomas, peculiarly located rheumatoid nodules, and the so-called myogeloses. The latter are indurations of voluntary muscles. Lange believes them to be the result of local chemical disturbances.[2] At operation the nodules were found situated (on the right side) on the lower portion of the sacrum near the ilium. A group of 6 nodes was removed from this area. They were composed of lobules of fat, each covered with a thin capsule. Both on gross and microscopic examination, their appearance was that of normal adipose tissue. No indications of inflammatory changes were present. Appropriate stains for nerve tissue showed nothing additional.

Soon after the operation the patient stated her complete relief from all previous symptoms. She was last seen 3 months after the operation, but did not return for additional treatment. No adequate reason for the disappearance of her complaint can be deduced on the basis of the tissue examination. It is hard to conceive what relationship these nodes could have borne to the low back pains.

In an effort to elucidate the concept proposed by Stockman that inflammatory changes in the subcutaneous fat could be a cause of

low back pain, it was decided to remove nodes from patients with obvious foci of infection.

CASE 2 (Admission No. 44950).—The patient, a male, aged 26, has had tuberculosis of the left astragalus for 3 years. In addition to this, clinical examination revealed the presence, bilaterally, of firm, pea-sized subcutaneous nodules over the sacroiliac areas. Low back pain was not present, nor was there any previous history of this complaint; the nodules were tender on palpation,

A subastragaloid arthrodesis was performed. At the same time, a cluster of small nodules was removed from over the left sacroiliac joint. They were composed of adipose tissue, enclosed in delicate capsules. Microscopic examination merely confirmed the gross findings; no evidence of either recent or previous inflammation was disclosed; the thin capsules showed the presence of small arterioles.

FIG. 2.—Photograph of the subcutaneous nodules removed from the sacroiliac area. They consist of lobules of adipose tissue.

CASE 3 (Admission No. 49221).—The patient, male, aged 42, complained of low back pain of 8 years' duration. Various therapeutic measures gave no relief. Clinical examination revealed limitation of forward and lateral movement of the trunk. Neurologic examination was negative. Stumps of tonsillar tissue were infected, and advanced pyorrhea alveolaris was present. Several small subcutaneous nodes could be palpated about 3 inches to the left of the third lumbar spinous process. Although freely movable under the skin, they appeared to be attached to the lumbar fascia. The tenderness in the lumbar and sacroiliac regions was concentrated over the nodes. Roentgenograms of the bones showed arthritic changes in the sacroiliac and lumbar joints.

With a view toward correlating the subcutaneous nodes and the infected tonsils, the nodes were removed. They, too, were found composed of lobules of fat enclosed in thin capsules. The histologic examination showed normal adult fat and a complete absence of any inflammatory changes. The tonsillar stumps were removed one week later. The low back pain still persisted, however, but the area previously tender on palpation was so no longer.

It was further decided to remove nodes from a case which had received no previous local physiotherapy.

CASE 4 (Admission No. D9753).—The patient, a colored woman, aged 29, complained of pain, recent in origin, in the sacroiliac regions, especially

the left. Except for a history of repeated sore throat, her anamnesis presents nothing remarkable. Clinical examination revealed slight limitation of the mobility of the trunk; there was no hamstring spasm; neurologic examination was negative. Tenderness was elicited on palpation of the left sacroiliac region. On less vigorous palpatory examination, groups of subcutaneous nodes could be distinguished bilaterally. Those in the region of the left sacroiliac joint were markedly tender. Radiographic examination of the pelvis disclosed arthritic changes in the joints. The patient had had no physiotherapy.

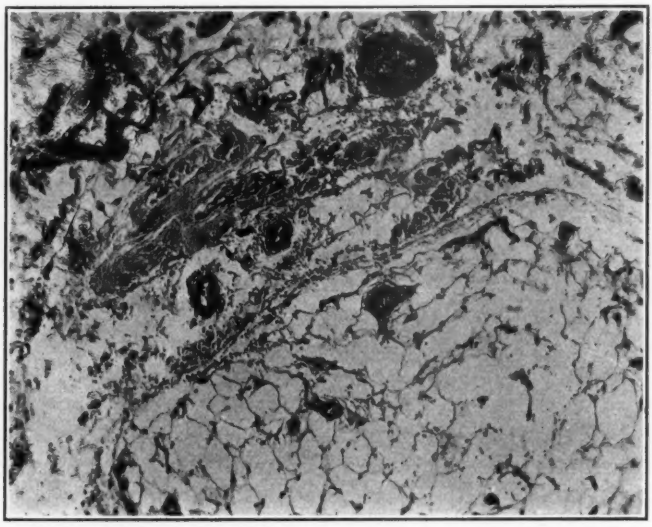

FIG. 3.—Photomicrograph shows the subcutaneous nodes to be normal adipose tissue covered by vascular capsules (× 100).

The nodes on the left side were removed under local anesthesia. On exposure they were found lying over the distal third of the sacrum close to the posterior inferior spine of the ilium. They were composed of fat and were encapsulated by connective tissue (Fig. 2). The microscopic examination confirmed the gross findings, the fat being normal adult fatty tissue and presented no inflammatory changes (Fig. 3). The clinical complaint did not subside after the operation.

Discussion. As is evident from the pathologic examination of the subcutaneous nodules removed from the sacroiliac regions of several patients, such nodules are composed of lobules of adult fat. The fatty tissue evidences no abnormality, nor is there any indication of inflammation or other evidence that could relate their origin to metabolic or toxic disturbance.[3] It would seem that the aforementioned subcutaneous nodules are probably protective or buffer pads over some of the poorly muscle-covered areas of the sacrum and ilium. Their occurrence is not associated with any recognized disease process, and they may be found in apparently normal persons.

Tenderness, often of exquisite degree, over the sacroiliac joints

may be attributed to the mere presence of these subcutaneous fat nodules and not to intrinsic disease in the joints. Of course, in Dercum's disease, lipomas may exist in the sacroiliac regions and cause intense pains of a neurogenic basis. The presence of additional large symmetrical fatty tumors in other parts of the body (in Dercum's disease) helps in differential diagnosis. The subcutaneous nodes discussed in this communication are wholly different from those of rheumatic fever, rheumatoid arthritis, syphilis, and so forth.[4]

The author is indebted to Dr. H. L. Jaffe for many helpful suggestions and to Doctors Finkelstein and Frauenthal for permission to operate on these 4 patients.

BIBLIOGRAPHY

1. Stockman, R.: Edinburgh Med. J., **15**, 107, 223, 1904.
Stockman, R.: Brit. Med. J., **1**, 352, 1911.
Stockman, R.: Rheumatism and Arthritis, Edinburgh, W. Green & Son, Ltd., 1920.
Stockman, R.: Brit. Med. J., **1**, 293, 1928.
Hausberger, F.: Zeit. f. Mik.-Forsch., **36**, 231, 1934.
2. Wood, W.: Trans. Med. Chir. Soc., Edinburgh, **3**, 317, 1829.
Goebel, C.: Centralbl. f. allg. Path., **6**, 4, 1895.
Jones, R. L.: Arthritis Deformans, New York, William Wood & Co., 1909.
Klinkowstein, J.: Med. Klin., **34**, 1307, 1911.
Daniel, P.: Inflammatory Diseases of Joints, New York, William Wood & Co., 1911.
Schmidt, A.: Der Muskelrheumatismus, Bonn, A. Marcus and E. Webers, 1918.
Coates, V., and Coombs, C. F.: Arch. Dis. Child., **1**, 183, 1926.
Dausset, H., and Lucy, A.: Gaz. méd. de France, **3**, 3, 1929.
Behrend, M.: Am. J. Surg., **7**, 857, 1929.
Fernandez, A. A.: Semana méd., **1**, 340, 1930.
Lange, M.: Die Muskelharten, München, J. F. Lehmanns, 1931.
Clawson, B. J., and Wetherby, M.: Am. J. Path., **8**, 283, 1932.
Adair, F., Pack, G., and Farrior, J. H.: Am. J. Cancer, **16**, 1104, 1932.
Rolleston, Sir H.: Brit. Med. J., **1**, 1033, 1933.
3. Telling, M. H. M.: Lancet, **1**, 154, 1911.
Bain, N.: Ibid., **1**, 363, 1912.
Auerbach, S.: Headache, London, Oxford University Press, 1913.
Cummings, F. A.: Boston Med. and Surg. J., **181**, 236, 1919.
Hunter, C.: Canad. Med. Assn. J., **16**, 1319, 1926.
Goldscheider: Deutsch. med. Wchnschr., **53**, 1669, 1927.
Williams, M. F.: Lancet, **1**, 720, 1928.
Coates, V.: Med. J. and Rec., **126**, 409, 1930.
Mella, H.: U. S. Vet. Bur. Med. Bull., **6**, 697, 1930.
Fitch, W. E.: Med. J. and Rec., **132**, 132, 1930.
Albee, F. H.: Am. J. Surg., **23**, 70, 1934.
4. Futcher, T. B.: Bull. Johns Hopkins Hosp., **6**, 133, 1895.
Parkes Weber, F., and Gray, A. M. H.: Brit. J. Dermatol., **36**, 544, 1924.
Brooks, B., and Lehman, E. P.: Surg., Gynec. and Obst., **38**, 587, 1924.
Rolleston, Sir H.: Brit. J. Dermat. and Syph., **36**, 407, 1924.
Jordan, A.: Dermat. Ztschr., **45**, 263, 1925.
Grieg, D. M.: Edinburgh Med. J., **35**, 565, 1928.
Christian, H. A.: Arch. Int. Med., **42**, 338, 1928.
Huguenin, R., and Albot, G.: Ann. d'anat. path., **7**, 497, 1930.
Brunsting, L. A.: Am. J. Syph., **15**, 42, 1931.
Shelley, H. J.: Arch. Surg., **23**, 513, 1931.
Swartz, J. H., and Tolman, M. M.: Arch. Dermat. and Syph., **26**, 418, 1932.
Low, R. C.: Edinburgh Med. J., **39**, 154, 1932.
Mair, W. F.: Ibid., p. 13.
Gottron, H.: Arch. f. Dermat. u. Syph., **166**, 584, 1932.
Lindberg, K.: Acta med. Scandin., **77**, 455, 1932.

BOOK REVIEWS AND NOTICES

GYNECOLOGICAL AND OBSTETRICAL TUBERCULOSIS. By EDWIN M. JAMESON, B.S., M.D., Fellow of Trudeau Foundation; Attending Surgeon, Saranac Lake General and Reception Hospitals. Pp. 256; 31 illustrations. Philadelphia: Lea & Febiger, 1935. Price, $3.50.

DR. JAMESON has divided his presentation of this somewhat neglected subject into three main parts, namely: the influence of pulmonary tuberculosis upon the genital physiology, the infections of the genital organs and peritoneum, and the problem of pregnancy in a tuberculous woman. The personal experiences of the Saranac group are incorporated in the study, together with a review and comparison of the ideas and results of other authors. The bibliography is unusually comprehensive. A series of experiments dealing with the routes of infection of the genitalia in animals is described. The author believes the possibility of an ascending type of infection must be taken into serious consideration. The need for premenstrual diagnostic curettage is emphasized. The use of Roentgen ray and radium treatment of pelvic tuberculosis is discussed. The section on pregnancy and tuberculosis reflects a conservative attitude toward the routine interruption of pregnancy, discusses the effects of collapse therapy, and other measures, and furnishes in the conclusions regarding treatment a set of excellent working rules for the physician who meets but an occasional instance of pregnancy and tuberculosis. The scope of the book, the well reasoned deductions, and the clarity of expression will serve to make this book widely read. P. W.

FREE MEDICAL CARE (SOCIALIZED MEDICINE). Compiled and Edited by E. C. BUEHLER, Director of Forensics, University of Kansas. Pp. 360. New York: Noble and Noble, Publishers, Inc., 1935. Price, $2.00.

THE most important non-professional question for medical men of our time is unquestionably that of socialized medicine and its associated problems. Willy-nilly each physician must take his stand on the subject; but unfortunately many do so under a maximum influence of emotion and a minimum of knowledge of the available facts. This book makes a worthwhile effort to supply this want in an impartial way. It should be valuable not only for the student debaters for whom it was primarily prepared, but also for the chronic debaters in organized medical societies and even for practitioners and medical students seeking unbiased information and arguments on both sides of this complex question. E. K.

MODERN HOME MEDICAL ADVISER. Your Health and How to Preserve It. Edited by MORRIS FISHBEIN, M.D., Editor, Journal American Medical Association, with 23 Collaborators. Pp. 905; 140 illustrations, 4 in color. Garden City N. Y.: Doubleday, Doran & Co., Inc., 1935. Price, $9.50 (bound in fabrikoid).

HERE is the old "medical book," well known in most homes of a few decades ago, brought thoroughly up to date. Not like its forerunners, given to suggest self-diagnosis and self-treatment to the layman, it is "planned to answer questions concerning all the common, and even some of the extraordinary, illnesses that may develop in any family . . . planned

also as an adequate guide to hygiene and first aid." The 33 chapters also cover such topics as Choice of a Physician, Sex Hygiene, Care of Mother Before and After Childbirth, The Hazards of Industry, Advice on the Diet, Nervous and Mental Disorders, Old Age. In addition to Dr. Fishbein there are 23 contributors, eminently qualified to handle their particular subjects, and including such well-known authorities as Elliott P. Joslin, Russell M. Wilder and Francis Carter Wood. Physicians will welcome this book, written in language that anyone can understand, as one they can heartily recommend to all laymen. Minor query: why not state the degree of magnification used in the picture of the Black Widow Spider (*Latrodectus* misspelled in text)? R. K.

THE PROBLEM OF MENTAL DISORDER. A Study Undertaken by the Committee on Psychiatric Investigations, National Research Council. Members of the Committee: MADISON BENTLEY, Chairman, Sage Professor of Psychology, Cornell University, and E. V. COWDRY, Professor of Cytology, Washington University. Pp. 388. New York: McGraw-Hill Book Company, Inc., 1934. Price, $4.00.

THIS volume was made possible through a grant of the Carnegie Foundation and through the excellent editorship of Professors Bentley and Cowdry —neither a psychiatrist, but both pure scientists, first-rank psychologist and cytologist respectively, and both well able to speak of psychiatry and its supportive sciences. It is these latter for which the bulk of this book is reserved. The first section, "The Character of the Problem," is a well written statement of the status of present-day psychiatry in all its manifold aspects, and of the suggested outlines of methods for solving its problems. Section Two, "Current Points of View," is an exposition of contemporary viewpoints of psychiatric thought, each propounded by an eminent representative; namely, C. MacFie Campbell ("Clinical"), A. Meyerson ("Medical"), I. S. Wechsler ("Neurological"), A. Meyer ("Psychobiological"), and L. S. Kubie ("Psychoanalytical"). Within Section Three, "Supporting Sciences: Present-day Contributions and Future Research," are compressed 20 short contributions by investigators in the sciences, including anatomy, physiology, chemistry, genetics, education, sociology and anthropology, etc. With the ambits of psychiatric theory and research continuously expanding, and with the anatomizing of related knowledge into even more complex secondary problems, such a critique does great service in bringing together the accumulated, unwieldy mass of uncorrelated data into the semblance of an intelligible whole, and in providing some measure of comforting orientation in the midst of confusion. This book deserves a wide distribution. There is an adequate index. P. R.

AN OUTLINE OF IMMUNITY. By W. W. C. TOPLEY, M.A., M.D., F.R.C.P., F.R.S., Professor of Bacteriology and Immunology in the University of London. Pp. 415; 37 illustrations and 63 tables. Baltimore: William Wood & Co., 1933. Price, $6.00.

THE author intended this book for the medical student, believing that "ignorance of the present working hypotheses of immunity means inability to form a sound judgment on many severely practical problems." The subject matter reveals incisive and comprehensive thinking. So careful is the presentation and criticism of data that it will be of service to the life-long student of medicine who also practises it. The Reviewer wishes particularly to commend the method of presentation. The first subject to be considered, and one too often neglected, is the nature and significance of the evidence obtainable in this difficult field, and the necessity in many

cases for the application of simple statistical methods in the criticism of results and the planning of experiments. Neglect of this has vitiated many a series of experiments. Without such a criterion it may be impossible to evaluate the therapeutic usefulness of a serum where the effect is not dramatic. The history of the use of antipneumococcal serum is a case in point (pp. 366–369). About a hundred pages are devoted to a useful summary of methods of standardizing immunologic reagents and their use in the diagnosis, treatment and prevention of disease. The practitioner should note that the book appeared in 1933, and therefore, is not always up to date. Suggestive work on the streptococci in puerperal fever, for instance, has since been done (p. 111). D. S.

A SYNOPSIS OF REGIONAL ANATOMY. By T. B. JOHNSTON, M.B., CH.B., Professor of Anatomy, University of London, Guy's Hospital Medical School. Pp. 460; 11 illustrations. Third edition. Philadelphia: Lea & Febiger, 1935. Price, $4.50.

THIS third edition represents little change from previous editions. The glossary of the B.N.A. has been revised and is probably one of the most useful sections of the book. The anatomy is discussed by regions with no illustrations, except 11 line drawings of the anatomy of the central nervous system. The book should be useful as a quick reference for students and practitioners. L. F.

NEW BOOKS.

Clinical Parasitology and Tropical Medicine. By DÁMASO DERIVAS, B.SC. BIOL., M.S., M.D., PH.D., Professor of Parasitology in the Graduate School of Medicine and Assistant Professor in the Department of Pathology, University of Pennsylvania; Pathologist to the Pennsylvania Department of Health, The Friends' Hospital, and the Skin and Cancer Hospital, Philadelphia, etc. In Collaboration with CARLOS T. DERIVAS, B.A., M.D., Pathologist to the Santo Tomas Hospital, Panama, etc. Pp. 367; 144 illustrations and a colored plate. Philadelphia: Lea & Febiger, 1935. Price, $5.00.

Body Water. The Exchange of Fluids in Man. By JOHN P. PETERS, M.D., Professor of Internal Medicine, Yale University School of Medicine. Pp. 405; 5 illustrations and 15 tables. Springfield, Ill.: Charles C Thomas, 1935. Price, $4.00.

Modern Home Medical Adviser. Your Health and How to Preserve It. Edited by MORRIS FISHBEIN, M.D., with 23 Collaborators. Pp. 905; 140 illustrations, 4 in colors. Garden City, N. Y.: Doubleday, Doran & Co., Inc., 1935. Price, $9.50 (bound in fabrikoid). (Review, p. 838.)

Beitrag zur Kenntnis des Ileum Terminale Fixatum und Ileus Ilei Terminalis Fixati. Eine anatomische, klinische und klinischstatistische Studie. (Vol. 75, Supp. 32 of Acta chirurgica Scandinavica.) By LENNART PETERSON. Pp. 113; illustrated. Helsingfors: Mercators Tryckeri Aktiebolag, 1934. (No price given.)

Free Medical Care (*Socialized Medicine*). Compiled and Edited by E. C. BUEHLER, Director of Forensics, University of Kansas. Pp. 360. New York: Noble and Noble, Publishers, Inc., 1935. Price, $2.00. (Review, p. 838.)

Grundzüge der praktischen Seelenheilkunde. By DR. MED. FRITZ KÜNKEL, Berlin. Pp. 168. Stuttgart: Hippokrates Verlag G.M.B.H., 1935. Price, Rm. 6.75, paper binding; Rm. 8, linen binding.

International Clinics. Vol. III, Forty-fifth Series, 1935. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with 14 Collaborators. Pp. 337; illustrated. Philadelphia: J. B. Lippincott Company, 1935.

One medical and three surgical papers, together with progress articles on ophthalmology and otolaryngology comprise this number. The International element is maintained by Parkes Weber's "Carcinoma Telangiectaticum" and Loeser's (of Freiburg) paper on the pituitary and thyroid.

A Textbook of Bacteriology. By THURMAN B. RICE, A.M., M.D., Professor of Bacteriology and Public Health at the Indiana University School of Medicine. Pp. 551; 121 illustrations. Philadelphia: W. B. Saunders Company, 1935. Price, $5.00.

Individual Exercises. Selected Exercises for Individual Conditions. By GEORGE T. STAFFORD, M.S., Director, Corrective Physical Education, University of Illinois, HARRY B. DECOOK, M.A., Director, Corrective Physical Education, Northwestern University, and JOSEPH L. PICARD, M.S., Director, Corrective Physical Education, University of Arizona. Pp. 111; 100 illustrations. New York: A. S. Barnes & Co., Inc., 1935. Price, $1.00.

"In recent years the question of exercise has become of vital interest. It is not unusual for a physician to prescribe 'exercise' as well as medicine. Individuals of their own accord are seeking health through exercise. School boards consider physical education as an integral part of education—rather than a frill or a fad. The difficulty comes in determining what kind, type or amount of exercise one should take. . . . Hence, this book is written, avoiding technical language as far as possible, with the idea of giving the reader basic information regarding exercise for *individual* needs. . . . The doctor, the physiotherapeutist, the physical educator and the teacher will find this book helpful in selecting exercises for the large number of individuals who, because of physical defects, deformities, etc., should not be permitted (or are not able) to take the regular physical education work." (From Authors' Preface.)

Mechanics of Normal and Pathological Locomotion in Man. By ARTHUR STEINDLER, M.D., F.A.C.S., Professor of Orthopedic Surgery, The State University of Iowa, Iowa City. Pp. 424; illustrated. Springfield, Ill.: Charles C Thomas, 1935. Price, $8.00.

The Stomach and Duodenum. By GEORGE B. EUSTERMAN, M.D., F.A.C.P., Head of Section in Division of Medicine, The Mayo Clinic; Professor of Medicine, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota, and DONALD C. BALFOUR, M.B., M.D. (TOR.), LL.D., F.A.C.S., F.R.A.C.S., Head of Section in Division of Surgery, The Mayo Clinic; Professor of Surgery, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota, and Member of the Staff, The Mayo Clinic and The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. Pp. 958; 436 illustrations. Philadelphia: W. B. Saunders Company, 1935. Price, $10.00.

A Marriage Manual. A Practical Guide-Book to Sex and Marriage. By HANNAH M. STONE, M.D., Medical Director of the Birth Control Clinical Research Bureau and of the Marriage Consultation Centers at the Community Church and Labor Temple, New York, and ABRAHAM STONE, M.D., Adjunct Urologist at the Sydenham Hospital, Co-Director of the Marriage Consultation Centers at the Community Church and Labor Temple, New York. Pp. 334; 8 illustrations. New York: Simon and Schuster, 1935. Price, $2.50.

Radium Treatment of Skin Diseases, New Growths, Diseases of the Eyes and Tonsils. By FRANCIS H. WILLIAMS, M.D. (HARV.), S. B. Massachusetts Institute of Technology; Senior Physician, Boston City Hospital; Fellow of American Academy of Arts and Sciences, etc. Pp. 118; 12 illustrations. Boston: The Stratford Company, 1935. Price, $2.00.

Diabetes, The Malady of Our Time. A Manual. Etiology, Course and Treatment of "Diabetes Mellitus." By DR. LEVY-LENZ and DR. HEINZ SCHMEIDLER. Pp. 64; illustrated. Berlin: A. K. Verlag (Arthur Kirchner), 1935. Price, $1.15.

Genetics. By H. S. JENNINGS, Henry Walters Professor of Zoölogy and Director of the Zoölogical Laboratory in the Johns Hopkins University. Pp. 373; 70 illustrations. New York: W. W. Norton & Co., Inc., 1935. Price, $4.00.

Diseases of the Nose and Throat. For Practitioners and Students. By CHARLES J. IMPERATORI, M.D., F.A.C.S., Professor of Clinical Oto-laryngology, New York Post-Graduate Medical School, Columbia University, and HERMAN J. BURMAN, M.D., Instructor of Clinical Oto-laryngology, New York Post-Graduate Medical School, Columbia University. Pp. 723; 480 illustrations, some in colors. Philadelphia: J. B. Lippincott Company, 1935. Price, $7.00.

NEW EDITIONS.

The Pathology of Internal Diseases. By WILLIAM BOYD, M.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), DIPL. PSYCH., F.R.S. (CAN.), Professor of Pathology in the University of Manitoba; Pathologist to the Winnipeg General Hospital. Pp. 904; 335 illustrations. Second Edition. Philadelphia: Lea & Febiger, 1935. Price, $10.00.

Laboratory Methods of the United States Army. Edited by JAMES STEVENS SIMMONS, B.S., M.D., PH.D., Major, Medical Corps, U. S. Army; Director of Laboratories, Army Medical Center; Director of the Department of Preventive Medicine, Army Medical School. Associate Editor, CLEON J. GENTZKOW, M.D., PH.D., Major, Medical Corps, U. S. Army; Chief of the Division of Chemistry, Army Medical School. Approved by the Surgeon-General of the U. S. Army. Pp. 1089; 70 illustrations and 133 tables. Fourth Edition. Philadelphia: Lea & Febiger, 1935. Price, $6.50.

"Although the title of this work is 'Laboratory Methods,' its scope has been enlarged to include material other than strictly technical procedures. For example, in the section on Bacteriology, tables of classification and brief summaries of the more important characteristics of certain bacteria have been added; and the sections dealing with Protozoölogy, Helminthology and Entomology have been expanded and include illustrations of certain organisms. New sections, one dealing with Rickettsia and Filterable Viruses and another with Statistical Methods, have been added." (From Author's Preface.)

The Treatment of Diabetes Mellitus. By ELLIOTT P. JOSLIN, M.D. (HARV.), M.A. (YALE), Medical Director, George F. Baker Clinic, New England Deaconess Hospital; Clinical Professor of Medicine, Harvard Medical School; Consulting Physician, Boston City Hospital. With the coöperation of HOWARD F. ROOT, M.D., PRISCILLA WHITE, M.D., and ALEXANDER MARBLE, M.D. Pp. 620; 7 illustrations and 144 tables. Fifth Edition, revised and rewritten. Philadelphia: Lea & Febiger, 1935. Price, $6.00.

Personal and Community Health. By CLAIR ELSMERE TURNER, M.A., DR. P.H., Professor of Biology and Public Health in the Massachusetts Institute of Technology, etc. Pp. 680; 130 illustrations, 4 colored plates and 13 tables. Fourth Edition. St. Louis: The C. V. Mosby Company, 1935. Price, $3.00.

Diseases of the Skin. By FRANK CROZER KNOWLES, M.D., Professor of Dermatology, Jefferson Medical College; Dermatologist to the Jefferson, the Pennsylvania, the Presbyterian and the Babies' Hospitals, etc. Pp. 640; 240 illustrations and 11 plates. Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1935. Price, $6.50.

PROGRESS
OF
MEDICAL SCIENCE

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF
FRANKLIN G. EBAUGH, M.D.,
PROFESSOR OF PSYCHIATRY IN THE UNIVERSITY OF COLORADO,
AND
GEORGE JOHNSON, M.D.,
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FUNCTIONAL LOCALIZATION IN THE CEREBRAL CORTEX.

THE study of functional localization in the brain may properly be said to begin, along with most other beginnings in medicine, with Hippocrates. In his treatise on "Wounds of the Head" he described various kinds of fractures and warned against incisions into the brain so as not to produce convulsion on the opposite side of the body. Galen taught that the cerebrum is the organ of intelligence and conscious sensations and apparently did ablation experiments on the cortex to study its function. At this time, however, and for many centuries after Galen, the ventricles were considered to be the principal centers for localized function; thus the anterior contained imagination, the middle reason and the posterior memory. In the 17th century Willis made some significant observations on the concept of cerebral localization and during the same century Wepfer[1] first accurately described cerebral apoplexy and hemiplegia. It was not until the latter part of of the 19th century however that real progress in the study of cerebral function was made. The work of Hitzig and Fritsch,[2] and of Ferrier[3] on the electrical stimulation of the exposed cerebrum of the living animal marks the beginning of our modern views. The first effect of the work of these investigators led to extreme views of localization of function in which different motor and sensory areas were thought to be definitely circumscribed. Cortical diagrams were numerous with different centers plotted for various functions, each center specific in purpose and sharply separated from every other in a mosaic pattern.

The development from this concept of localization of function to sharply limited areas to the present-day concept is well expressed by de Barenne[4] in his criticism of the use of the term localization of function. He writes, "An enormous number of nervous activities involve not only the cortex but also other levels of the nervous systems. This is true of the human being, so far as is known, for all perceptual and

voluntary activity. This means, irrespective of one's point of view in regard to the problem of functional localization within the cortex, that it is incorrect to state that vision, hearing or motility is 'localized' in the cerebral cortex. If this term is used, the only appropriate statement would be that the nervous function under consideration is 'localized' in all those nervous structures which are thrown into activity in the performance of the function." The central nervous system has come to be looked on as a highly integrated mechanism each cell of which has a demonstrable function to perform not as an independent entity but as a unit essential for the successful operation of the mechanism as a whole.

Although this point of view has gradually developed during the past 60 years, notably through the contributions of Sherrington,[5,6] Beevor and Horsley,[7] Brodmann,[8] the Vogts,[9] significant contributions have been made during the past year especially in the studies of Fulton and his group on the frontal lobe.

The Frontal Lobe. From the standpoint of functional activity the frontal lobe may be divided into four well-defined areas. As defined by Fulton[10] these areas are:

1. The motor area beginning in the depths of the central sulcus and extending rostrally on the lateral surface. The limits of the motor area are determined by its cellular structure, being the region of the cortex containing in its fifth layer the large cells of Betz which give rise to the pyramidal pathways.[11]

2. The premotor area comprises the region of the cortex anterior to the motor area. It is histologically identical with the motor area apart from the absence of the large motor cells in the fifth layer. In man the premotor area occupies a much larger part of the exposed surface of the hemisphere than does the motor area.

3. The frontal eye fields. These are a specialized part of the frontal lobes, concerned with coördinated eye movements.

4. The frontal association areas, or the pre-frontal area.

The Motor Area: (Area 4). It is a time honored conception that a destructive lesion of the motor cortex always produces contralateral paralysis accompanied by heightened tendon reflexes, spasticity and finally contractures. Experimental evidence and clinical data cast considerable doubt upon this conception. Studies of the response to electrical stimulation of the motor cortex shows that the resultant movement is of a discrete type, generally one produced by a single muscle. The response is distinctly focal. Only if the stimulus is very strong or if the threshold stimulus is continued over a long period does the movement spread to adjacent muscles, producing the traditional "march" of the Jacksonian focal seizure. Furthermore, stimulation of a point at the anterior margin of the motor area produces movements of the ipsilateral lower extremity. In ablation experiments, a unilateral lesion sharply restricted to the motor area causes immediate and complete paralysis of voluntary movement for a period varying from 2 days to a week. During this period the limbs are flaccid with diminished or absent reflexes, and marked muscular wasting may appear. Voluntary motor power gradually returns, appearing first at the hip and the shoulder and gradually extending to the knee and ankle and finally to the digits. The deep reflexes gradually reappear. The

Babinski and Chaddock reflexes develop when the deep reflexes return. There is no loss of memory or mental confusion even when the pure motor area lesion is bilateral.

Premotor Area: (Area 6). From the point of view of electrical excitability, the premotor area may be divided into anterior and posterior parts (Areas 6a Alpha and 6a Beta). From the posterior part movements of individual muscles may be obtained which are similar but somewhat less discrete than those obtained from the premotor area. These discrete movements cannot be evoked after the motor area has been destroyed or after the cortex has been superficially incised between the motor and the premotor area: the movements are therefore dependent upon the integrity of the pyramidal fibers. From the entire premotor area, complex and seemingly purposeful movements are to be observed which effect not single muscles but an entire extremity or the whole half of the body. These responses involve patterns of movement rather than the reactions of single muscles. They are generally associated with turning the head and eyes to the opposite side and with torsion of the pelvis. All of this reaction persists after incision of the cortex between Areas 4 and 6 and after complete degeneration of the pyramidal tracts. They disappear when Area 6 is undercut. The reactions therefore clearly involve the extrapyramidal motor projection systems arising in the premotor area.[12,13] Following isolated removal of the premotor area profound motor disability occurs which lasts both in man and in the chimpanzee for 4 or 5 days. Immediately after such a lesion the affected extremity becomes highly spastic; no wasting occurs, electrical excitability is normal and certain characteristic pathologic reflexes such as forced grasping,[14] the fanning sign of Babinski and the sign of Rossolimo, Mendel, Bechterew and Hoffman develop. There is also profound vasomotor disturbance, the affected side losing for a time its power of reflex vasodilation and sweating.[15] Voluntary power begins to return simultaneously in all parts of the extremity generally in 4 or 5 days but skilled movements such as those necessary to play the piano, to finger a violin or to tie a shoe lace become permanently impaired.[16] In trained animals there is considerable intellectual deficit in that they forget problem box manipulations but reëducation is possible (Jacobsen[17,18]).

Frontal association area or pre-frontal area: No movements of the extremities or of any other of the bodily structures are obtained by stimulation of these areas. Removal of one frontal area causes no recognizable deficit, intellectual or neurologic unless the eye-fields are encroached upon in which case the animal is unable for about 48 hours to carry out conjugate lateral deviation of its eyes to the site of the lesion. Bilateral ablation of the frontal association areas is also without effect upon reflexes, motor power or posture but it has a profound influence upon the behavior and the capacity to learn and remember complex problems. The animal becomes very restless and easily distracted and previously acquired patterns of response in problem situations deteriorate and the animal cannot be retrained. No dominance of lobes is noted in lower animals. In summary, Fulton makes the following conclusions as a result of experiments on the cortex of trained monkeys and chimpanzees.

1. Electrical excitability is present in the motor, premotor and eye

fields but not in the frontal association area. The excitability of the premotor area persists after complete removal of the motor area and degeneration of the pyramidal tracts. Movements of the ipsilateral lower extremities can be obtained from the premotor region.

2. Ablation of the motor area causes flaccid paresis with depression of the reflexes. Voluntary power invariably returns however in all four extremities, after the motor area has been completely removed from both sides.

3. Ablation of the premotor area causes transient spastic paresis with forced grasping and increase in all the deep reflexes. Combined ablation of motor and premotor areas cause permanent spasticity as in capsular hemiplegia but not complete loss of power.

4. Removal of motor and premotor areas from both hemispheres is followed by complete and permanent loss of voluntary power (cortical paralysis) and the postural reflex status of such a preparation is identical to that of a thalamus animal.

5. If a part of one motor or premotor area of one hemisphere remains intact the animal is able to carry out cortically innervated movements in all four extremities. This, together with the observations on stimulation, indicates that ipsilateral representation exists in both the motor and premotor regions.

6. Removal of the premotor area gives rise to vasomotor disturbance on the opposite extremities and to other signs of impairment of the autonomic function.

7. Bilateral removal of the frontal association areas causes no paresis or reflex disturbance but it causes loss of memory for complex skilled acts and an incapacity to profit by recent experience.

In a summary of the clinical interpretations of these phenomena, Fulton and Viets[19] make the following conclusions:

1. Lesions restricted to the pyramidal tracts or to their cells of origin cause flaccid motor paralysis, muscle atrophy, transient depression of all reflexes and the positive signs of Babinski and Chaddock; after complete destruction of the pyramids, the signs of Babinski and Chaddock persist permanently but the paralysis flaccidity and reflex changes tend with time to disappear.

2. Lesions of the premotor projection area of the cortex, which also indicate voluntary movements give rise to spastic paralysis, disturbance of skilled movements, forced grasping, vasomotor disturbance, increased deep reflexes and the signs of Rossolimo, Mendel, Bechterew and Hoffman. Forced grasping and vasomotor disturbance are transient but disturbances of skilled movements and the signs of Rossolimo and Hoffman tend to persist.

3. Hemiplegia in man is generally produced by combined destructions of motor and premotor components of the upper motor neuron and hence such cases generally exhibit combinations of the foregoing symptoms with more severe ultimate motor paralysis than when only the pyramidal tracts are involved. The prognosis can be inferred from the extent to which the two systems are involved.

Aphasia. Another noteworthy contribution to the understanding of functional localization was the publication by Weisenburg[20] of the results of his 4-year study of aphasia. From a group of 314 patients 60 were selected for study on the basis of: Clearcut aphasia, age under 60, English as a mother tongue and adequate sight and hear-

ing. A comprehensive group of tests so designed as to cover a wide field of language and mental functioning was given to this group and to an additional control group of 85 normal adults, comparable to the aphasic group in age and in educational, occupational, and social classes. The most satisfactory classification of aphasic disorders according to this study is (*a*) the expressive, (*b*) the receptive, (*c*) the expressive-receptive, and (*d*) amnestic. Of the four the amnestic represents the only fairly clearcut syndromes. The disorders of the first two groups are only predominantly expressive or predominantly receptive; in the expressive there is always some degree of limitation in receptive functions and in the receptive there are always some defects in speaking and writing.

(A) The predominantly expressive disorders handicap speaking and writing more seriously than the receptive functions. They are characterized most obviously by defects in articulation and word formation but they may involve extensive changes in many language and non-language performances.

(B) The predominantly receptive disorders involve relatively serious defects in the understanding of spoken language or of printed material. Expressive disturbances also appear but are almost always less prominent than the receptive; they consist largely of verbal and grammatical confusions.

(C) The expressive-receptive disorder is a severe limitation in all language processes with or without considerable disturbances of non-language performances.

(D) The amnestic disorder is a fundamental difficulty in evoking words as names for objects, conditions or qualities and is manifested in many language responses. From this classification it is apparent that aphasia is not a unitary disorder but a group of disorders representing different types of disintegration within the language process and sometimes involving changes in mental functioning beyond the language process.

In this study the term apraxia was limited to disturbances in familiar and more or less automatic acts which do not depend on sensorimotor defects. Agnosia was limited to disturbances in the perception of formerly well known objects, forms and sounds when there are so sensory defects to explain the disturbances. There are two types of apraxia, one involving movements of the muscles of speech and the other familiar acts such as manipulating an object. Some of the aphasic patients were unable to take positions of the lips, teeth and tongue at command or by imitation when the production of actual sounds was not in question. The apraxic symptoms of the other type appeared in cases of general deterioration with aphasia or in cases of bilateral lesion.

Agnosic disturbances in the recognition of well known sounds other than speech sounds, of objects, or of forms other than letter symbols were not found in patients of the aphasic group. There is a definite dominance of the hemispheres not shown in lower animals as indicated by the evidence that the dominances indicated by handedness is a criterion of the crucial hemisphere for speech in about 95% of the cases. From the clinical symptomatology and pathologic evidence in the expressive cases, the lesions were predominantly in the anterior portion of the brain and to a less extent in the parietal and temporal zones. In the receptive cases as a group the neurologic symptoms also indicate

a preponderant implication of the anterior part of the brain, but less than in the expressive cases and with a greater involvement of the parietal and temporal zones. In the expressive-receptive cases, the neurologic symptoms point strongly to implication of the anterior part of the brain but because of the patient's great language difficulties little can be determined about the extent to which posterior areas are involved.

It is the opinion of Weisenburg that it is very much a question whether it will ever be possible to localize from the anatomic standpoint the causes which lead to aphasic disturbances. The disorders in aphasia go beyond speech disturbances, and the complex processes affected depend on the function of the whole brain.

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REFERENCES.

1. Wechsler, I. S.: A Text-book of Clinical Neurology, Third Edition, Phila., W. B. Saunders Company, 1935.

2. Fritsch, G., and Hitzig, E.: Ueber die elektrische Erregbarkeit des Grosshirns, Arch. f. Anat. u. Physiol. u. wissensch. Med., **37**, 300, 1870.

3. Ferrier, D.: Experimental Researches in Cerebral Physiology and Pathology, West Riding Lunatic Asylum Med. Repts, **3**, 1, 1873.

4. De Barenne, J. G. D.: A Word of Criticism on the Designation "Localization of Function in the Cerebral Cortex," Arch. Neurol. and Psychiat., **33**, 1081, 1935.

5. Langley, J. N., and Sherrington, C. S.: On Sections of the Right Half of the Medulla Oblongata and of the Spinal Cord of the Dog Which was Exhibited by Prof. Goltz at the International Medical Congress of 1881, J. Physiol., **5**, **6** (Proceedings), 1884.

6. Grünbaum, A. S. P., and Sherrington, C. S.: Observations on the Physiology of the Cerebral Cortex of the Anthropoid Apes, Proc. Roy. Soc., **71**, 55, 1903.

Grünbaum, A. S. F., and Sherrington, C. S.: Observations on the Physiology of the Cerebral Cortex of the Anthropoid Apes, Ibid, **72**, 152, 1903.

7. Beevor, A., and Horsley, V.: A Record of the Results Obtained by Electrical Excitation of the So-called Motor Cortex and Internal Capsule in an Orang-Outang (Simia satyrus), Philosophical Trans. Roy. Soc., p. 129, 1890, B. 181.

8. Brodmann, K.: Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Principin dargestellt auf Grund des Zellenbaues, x, p. 324 Leipsic, Barth, 1909.

9. Vogt, C., and Vogt, O.: Allegemeinere Ergebnisse unserer Hirnforschung, J. f. Psychol. u. Neurol., **25**, 276, 1919.

10. Fulton, J. F.: Paralyses of Cortical Origin, Proc. Calif. Acad. of Med., pp. 1–19, 1933–1934.

11. Bucy, P. C.: Frontal Lobe of Primates: Relation of Cyto-Architecture to Functional Activity, Arch. Neurol. and Psychiat., **33**, 546, 1935.

12. Hoff, E. C.: Corticospinal Fibers Arising in the Premotor Area of the Monkey: Distribution of Bouton Terminations, Ibid., p. 687.

13. Kennard, M. A.: Corticospinal Fibers Arising in the Pre-motor Area of the Monkey as Demonstrated by the Marchi Method, Ibid., p. 698.

14. Hines, M., and Richter, C. P.: The Production of the "Grasp Reflex" in Adult Macaques by Experimental Frontal Lobe Lesions, Assn. for Res. on Nerv. and Ment. Dis., Proc., **13**, 211, 1932.

15. Kennard, M. A.: Vasomotor Disturbances Resulting From Cortical Lesions, Arch. Neurol. and Psychiat., **33**, 537, 1935.

16. Kennard, M. A., Viets, H. R., and Fulton, J. F.: The Syndrome of the Premotor Cortex in Man: Impairment of Skilled Movements, Forced Grasping, Spasticity and Vasomotor Disturbance, Brain, **57**, 69, 1934.

17. Jacobsen, C. F.: The Influence of Motor and Premotor Area Lesions upon the Retention of Skilled Movements in Monkeys and Chimpanzees, Assn. for Res. on Nerv. and Ment. Dis., p. 225, 1934.

18. Jacobsen, C. F.: Functions of Frontal Association Area in Primates, Arch. Neurol. and Psychiat., **33**, 558, 1935.

19. Fulton, J. F., and Viets, H. A.: Upper Motor Neuron Lesions, J. Am. Med. Assn., **104**, 357, 1935.

20. Weisenburg, T. H.: A Study of Aphasia: The Charles K. Mills Memorial Lecture, Arch. Neurol. and Psychiat., **31**, 1, 1934.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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SUPPURATION OF THE PETROUS PYRAMID.

PETROSITIS, petrosal tip suppuration, and suppuration of the petrous pyramid are terms which have been applied to a syndrome occurring during the course of an acute otitis media or mastoiditis. The pathologic basis for the clinical picture is a suppurative process within the pneumatic cells of the petrous portion of the temporal bone, or an osteomyelitis of the pyramid. For years reports of inflammatory lesions located in the petrous pyramid have appeared in the literature. These in the main have been in the nature of unusual findings at autopsy of meningitis deaths of otogenic origin. Macroscopic and microscopic descriptions of various fistulæ leading from the middle ear to the meninges constituted the main body of the reports as a rule. For some reason the clinical symptomatology of such lesions, and what is more important, the clinical sequence of events that led to the terminal meningitis received but scant attention. It is true that the Gradenigo syndrome, consisting of pain in the distribution of the trigeminal nerve associated with external rectus palsy and otorrhea, has had extensive otologic recognition, and the occasional complication of meningitis was also well known. It remained for the classic and monumental work of Kopetsky and Almour[1] definitely to establish petrositis as a clinical entity by minutely describing the anatomic basis for the lesion, its specific pathology, its symptomatology and characteristic course, diagnostic criteria, and last, but not least, an operative technique for dealing effectively with the process in order that a fatal meningitis be prevented. Since that time suppuration of the petrous pyramid has assumed a deservedly prominent place in the otologic literature, as is evidenced by the large number of contributions dealing with the condition that have appeared all over the world in the past few years.

Anatomy. Examination of a well pneumatisized temporal bone discloses the fact that the pneumatic cells are not confined to the mastoid portion but are seen to invade the zygoma, the squama, the floor of the middle ear, the tegmen and also the petrous tip. These cells, occupying portions of the temporal bone other than the mastoid, bear the same developmental relationship to the middle ear as do the mastoid cells themselves, and for that reason can well become involved in a suppurative process originating in the middle ear. Most investiga-

tions have shown that the petrosal pyramid frequently presents a structure similar to that of the mastoid itself. Thus a well pneumasized mastoid process is frequently associated with a well pneumatisized petrosa, while diploic and sclerosed mastoids usually accompany similarly constituted petrous tips. Pneumatization of the petrous apex does not appear as frequently as has been supposed. Myerson[2] and his coworkers described such a condition in but 11% of 200 temporal bones studied. They also found that the cellular structure of the petrous pyramid and the mastoid were not always alike, as 25% of the mastoids were pneumatisized, as compared with the 11% of the tips. As the cases reported by Kopetsky and Almour occurred in fully pneumatisized mastoids associated with cellular petrous tips, the importance of these findings is obvious; for a non-cellular pyramid cannot undergo coalescence and contain within its anatomic confines a frankly purulent collection. Profant,[3] in a study of 50 adults, concluded that as a rule a well developed mastoid had a well developed petrous, and one with a sclerotic mastoid had a sclerotic petrous pyramid. Belinoff and Balan[4] found pneumatisized tips in 38% of 40 temporal bones studied. Hagens,[5] in a study of 25 bones in gross section and a similar number microscopically, found that 28% of the gross specimens had a pneumatisized apex. Ramadier[6] divides the cells into a intrapetrosal group and a supralabyrinthine group, and Lange[7] describes similar cell tracts.

Pathology. In the original report by Kopetsky and Almour,[1] the petrous lesion was described as a coalescent osteitis of the cells in the petrous tip, which they believed to constitute a distinct pathologic entity. The avenues of infection mentioned by them were: (1) From the antrum or epitympanic space, above or below the superior semicircular canal, following the postero-superior surface of the petrosal into the tip; (2) via the peritubal cells into the tip; (3) via the peritubal cells directly into the carotid canal or through dehiscences in the anterior tympanic wall into the carotid canal.

These avenues can be recognized macroscopically at postmortem or at the operating table. Microscopic examination disclosed the pathway to be along the perilabyrinthine cells originating in the antrum or epitympanum. Friesner and Druss[8] also mention the peritubal route. The end result of the spread of the infection is the development of an abscess or empyema of the petrous tip if it be cellular in nature. If, on the other hand, the tip is diploic in character an osteomyelitis will result, as has been described by Eagleton.[9] The extension of the inflammation to the superior surface of the tip involves the Gasserian ganglion with the production of the typical distribution of pain. A subdural abscess may develop, or, as frequently occurs, the lesion may spread to the meninges with the development of a fatal meningitis. The suppurative process appears to spread by way of the perilabyrinthine tracts, as the mastoid and middle ear infection tends to clear up and disappear. At times the petrous suppuration may discharge into the middle ear by rupturing through cells around the Eustachian tube. This fact can account for the characteristic observation in petrositis of the sudden occurrence of profuse discharge after an interval of a dry ear, and also explains some of the cases in which spontaneous cure has been observed.

Probably the most outstanding pathologic manifestation in petrous

suppuration is the fistulization leading from the middle ear or mastoid into the petrosa. It has been the subject of a great deal of interest in most reports that have dealt with the operative or autopsy findings in this condition. Myerson, Rubin and Gilbert[36] were able to collect 53 cases from the literature in which such fistulæ were observed and recorded. Twenty-nine of these tracts were found in relation to the superior semicircular canal, 18 were found in relation to the Eustachian tube, being located at the tubal orifice or peritubal. Five were found just below the posterior canal, 4 at the arch of the superior canal and 1 behind the posterior canal. We thus have a clue as to the probable location of a fistula and where it must be sought at the time of operation. The varying sites of the fistulæ may also explain why no one surgical procedure could be applicable to all cases.

Symptomatology. The characteristic picture of petrous suppuration is exhibited by a patient afflicted with a prior acute suppurative middle ear infection or mastoiditis, who complains of a pronounced and profuse recurrence of the otorrhea and the appearance of pain on the same side at about the same time. The pain, as a rule, is limited to the eye or the orbit and is described by the patient as in or back of the eye, the location and character being almost diagnostic in significance. There is present a low grade sepsis, the temperature ranging from 99 to 102°. The pain, discharge and sepsis, as a rule, appeared after a quiescent interval varying from 5 days to several weeks, during which no pain was present, and in which the ear had become dry or almost so and in which the temperature showed but little rise above normal. The Roentgen ray reveals two important findings, a highly pneumatisized mastoid and petrous tip and a suppurative lesion in the latter. It is to be noted that abducens paralysis is not mentioned and the lesion is therefore not to be confused with Gradenigo's syndrome as has frequently occurred in the reported literature. Perrone,[11] reporting 3 cases, states that only infrequently is the Gradenigo syndrome caused by a petrous suppuration. Takaski,[12] Retjo,[13] Mounier-Kuhn,[14] Ballenger,[15] and Piquet,[16] all report cases with abducens palsy but with no evident petrosal lesions. Yet external rectus paralysis does occur in some cases of petrositis, as evidenced by the reports of Lemaitre and Lemoine,[17] Seydell,[18], Blassingame,[19] Bernstein,[20] Galtung,[21] Ruttin,[22] and Moulonguet and Pierre.[23] Undoubtedly the appearance of the rectus lesion was an expression of meningeal involvement from the suppurating petrous pyramid. Apparently petrosal suppuration may occur with or without abducens paralysis. The explanation of the pain in and about the eye was that it was consequent to an irritation of the ophthalmic branch of the fifth nerve. Studies by Vail[24] led him to believe that the pain was caused by the great petrosal nerve rather than the ophthalmic branch of the trigeminal. Eagleton,[9] however, explained the irritation of the ophthalmic branch of the fifth nerve as being due to tension on the dura surrounding the nerve by the edema and swelling consequent to the inflammatory process in the adjacent bone. Myerson and his coworkers[10] believe that the recurrent tentorial branch of the ophthalmic division to be the explanation of the phenomenon. Paralysis of the seventh nerve has been described, Myerson *et al.* having 3 cases and Kopetsky,[1] Profant,[3] and Friesner and Druss,[8] also report such cases. The discharge as a rule is profuse, although it may be

scant or absent. The discharge is large in amount when a fistulous tract from the petrous is emptying the exudate into the middle ear or mastoid. If the fistula is blocked by granulations the otorrhea diminishes and becomes scant or absent. If no fistula is present little, if any, otorrhea may be seen. As the suppuration is contained within the perilabyrinthine cells it is not unusual to find some cases evidencing symptoms of labyrinthine irritation. These are usually vertigo and nystagmus. Functional examination of the labyrinth is negative, showing the lesion to be a perilabyrinthitis. The laboratory findings are those of a mild infection. A leukocytosis of 9000 to 14,000 may be present. The organisms responsible for the infection are similar to those found in any mastoid infection. Rollin[25] and Fowler[26] report petrous infections due to the well known virulent pneumococcus Type III.

The Roentgen ray is of great importance and must be considered one of the guiding signs in the management of the disease. Caution must be exercised in the interpretation of the Roentgen ray films. Sussman[27] believed that the picture taken in the Stenver position was most useful. Epstein[28] preferred 3 exposures by the methods of Schuller, Mayer, and Stenver. Probably the method of Taylor[29] is the safest to follow. He takes a base plate showing both petrous tips early in the course of the otitis and files this for future reference. If later in the course significant clinical phenomena appear, another base plate and a Stenver plate are taken. By comparison with the early base plate, significant changes in the petrosa may be established.

Treatment. The therapy of petrous suppuration is surgical. The manner of approach and the type of surgery to employ must vary somewhat with the nature of the lesion. Whatever method is undertaken, it is assumed that it must be adequate in eradicating the suppurating focus and preventing extension of the disease to the meninges with a possibly fatal outcome. Various techniques have been advocated. Voss[30] believed that, in addition to the performance of the mastoid exenteration, a wide exposure of the epitympanum would be sufficient to drain the petrosa. Undoubtedly the exposure of a fistula without enlarging its opening will but rarely cause it to drain satisfactorily. Many cases in which no apparent fistula can be observed have been described and such cases of course require further surgery. This type of surgery is certainly far from convincing as to its adequacy in the various types of purulent retention in the petrous pyramid. Frenckner[31] enters the petrous tip through the arch of the superior semicircular canal, removing the cancellous tissue between the horizontal and superior canals with a specially constructed curette, outlining the arch and following the cells beneath the arch, forward and inward until the tip is entered. If a fistula is present at the time of operation, it would seem wiser to utilize this tract established by Nature to drain the tip by widening and enlarging it. Even when confronted by a closed empyema of the tip, this procedure may be found wanting as the presence of a tract of cells beneath the arch is not constant and one may have extreme difficulty in producing a tract through the dense bone. Ramadier, Guillon and Becker[32] describe a rather formidable procedure which they developed on the cadaver. The technique entails an extensive wide radical mastoid operation, removing the anterior bony

canal wall as well as the floor, exposing the glenoid fossa and the anterior wall of the middle ear which is removed below the opening of the Eustachian tube, thus exposing the carotid artery which is pulled out of its canal by means of a ligature, enabling the operator to enter the petrous tip through the inner wall of the carotid canal. Such a radical procedure is open to a serious question. The mandibular joint may have interference with its function as a result of the operation. Postoperative drainage from the tip may be impeded by the carotid artery falling back into place at the termination of the procedure, and the technique may also open other pathways of septic soilage of the meninges by way of the perivascular spaces. In the presence of an obvious fistula one can hardly see the need of such an extensive and radical procedure, fraught with such possibilities just mentioned. Eagleton[33] skeletonizes the posterior aspect of the petrous bone by the removal of the sinus plate, the tegmen, the bone over Trautmann's triangle and then removes the root and some of the zygoma, the squama and some of the anterior canal wall, thus skeletonizing the anterior portion of the petrosa. The tegmen is then completely removed and the dura elevated, bringing the petrous tip into view, which is entered by removing the bone overlying the apex. Almour[1] has developed a logical technical approach that is especially indicated for drainage of an empyema of the tip in a pneumatisized petrous pyramid in which no demonstrable fistula is evident. Following a radical mastoid operation the tensor tympani muscle is removed and the orifice of the Eustachian tube identified. Then by means of a drill a tract is made by placing the burr point in the roof of the mouth of the Eustachian tube and burring inward and forward at an angle of 22 degrees to the external canal. This technique in forming a tract along the peritubal cells gives adequate, dependent drainage to the tip. Further, it seems to follow the path that has been so frequently described in many cases in which a spontaneous fistula has been affected by Nature. It is obvious that any of these techniques may not be necessary as a rule in cases in which at the time of operation a fistula had been found either in the epitympanum or in the middle ear. In such instances, probably all that is necessary is the widening and curettement of the established tract so as to afford efficient drainage. Lillie[34] has reported 2 such cases in which cures were effected by widening and curettement of a fistula that appeared in the epitympanum, and Seydell[35] reports similar success in the use of this procedure.

Myerson, Rubin and Gilbert[36] advocate entry into the anterior wall of the petrous tip by means of a special gouge, after the performance of a thorough simple mastoid operation. They claim that their procedure effects a thorough evacuation of the petrous tip with preservation of the patient's hearing. In another contribution[37] on the subject they point out the frequent bottle-neck arrangement of the fistula which they believe would at times preclude efficient drainage and therefore advocate uncapping of the anterior wall of the pyramid.

A review of the recorded cases makes it obvious that no one of the procedures described is equally applicable in all cases. It would appear logical to perform first an extensive and thorough simple mastoid operation and then search for the presence of a fistula at the sites of predilection: either anterior or posterior to the superior semicircular canal,

either within or above the arch of the superior semicircular canal, and either below or posterior to the posterior canal. If a fistula be found at any of these sites it might be widened and enlarged and the patient carefully observed. If the postoperative progress was unsatisfactory, then the petrosa might be entered and the tip uncapped. If, however, no fistula is found, the simple mastoid cavity might be converted into a radical mastoid cavity and search made for a fistula either at the Eustachian tube orifice or just above it. A fistula found in this region is treated by enlarging and widening its tract and careful postoperative observation will decide as to the adequacy. If no fistula is found at this time, then recourse to a more radical procedure is necessary. Here one may have his choice of those suggested by Almour, Eagleton, or Myerson and his associates.

The exact indication for surgical intervention on the petrous pyramid has not as yet been definitely determined and a great deal of confusion still exists.

Certainly not all cases of petrosal involvement require surgery. It is conceivable that the petrous tip may be but mildly involved in the pathologic process and it has probably been the experience of most otologists that many of their cases of mastoiditis with pain in and about the eye have gotten well without a petrous operation. In fact, Myerson[36] states that about 80% may recover with conservative management. Yet the potential complications of meningitis, brain abscess, cavernous sinus thrombosis and general sepsis are of such a grave and frequently fatal nature as to make us profoundly conscious of our responsibility when confronted by a case of petrosal infection. While no hard and fast rule may be drawn, conservative management seems to be indicated only in those cases in which the pain is mild and decreasing in intensity, in which the temperature is normal, or slightly elevated, in which the discharge has not abruptly ceased and in which the Roentgen ray findings show either a normal or a slightly involved petrous tip. On the other hand, pain increasing in intensity, especially if it be nocturnal and interfere with sleep, a rising temperature, a sudden cessation of the discharge, positive Roentgen ray findings, and signs of sepsis or meningeal irritation all point to an immediate evacuation of the petrous tip as a means of preventing further progression of the purulent process towards the cranial cavity with the possible production of a fatal complication. The danger lies, not in the operation, but in the delay during which meningitis, brain abscess or cavernous thrombosis may supervene.

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REFERENCES.

1. Kopetsky, S. J., and Almour, R.: Ann. Otol., Rhinol. and Laryngol., **39**, 996, 1930; **40**, 157, 396, 922, 1931.
2. Myerson, M. C., Rubin, H. W., and Gilbert, J. G.: Arch. Otolaryngol., **20**, 195, 1934.
3. Profant, H. J.: Ibid., **13**, 347, 1931.
4. Belinoff and Balan, M.: Monatschr. f. Ohrenh., **64**, 1185, 1930.
5. Hagens, E. W.: Arch. Otolaryngol., **19**, 556, 1934.
6. Ramadier, J.: Ann. d'oto-laryngol., p. 1300, December, 1931.
7. Lange, W.: Ztschr. f. Hals-, Nasen- u. Ohrenh., **32**, 99, 1932.
8. Friesner, I., and Druss, J. G.: Arch. Otolaryngol., **12**, 342, 1930.
9. Eagleton, W. P.: Arch. Surg., **2**, 386, 1930.

10. Myerson, M. C., Rubin, H. W., and Gilbert, J. G.: Arch. Otolaryngol., **22**, 62, 1935.
11. Perrone, P.: Ann. di laryng. Otol., **33**, 32, 1933.
12. Takaski, M.: Otologia (Fukuoka), **6**, 681, 1933.
13. Retjo, A.: Monatschr. f. Ohrenh., **67**, 1247, 1933.
14. Mounier-Kuhn, P.: Zentralbl. f. Hals-, Nasen- u. Ohrenh., **22**, 128, 1934.
15. Ballenger, H.: Ibid., **21**, 780, 1934.
16. Piquet, J.: Ibid., p. 727, 1933.
17. Lemaitre, F., and Lemoine, J.: Ibid., **22**, 445, 1934.
18. Seydell, E. M.: Trans. Am. Laryn. Otol. and Rhin. Soc., p. 561, 1933.
19. Blassingame, C. D.: Ibid., p. 480.
20. Bernstein, S.: J. Laryngol. and Otol., **48**, 196, 1933.
21. Galtung, A.: Norsk mag. f. lagevidensk., **94**, 625, 1933.
22. Ruttin, E.: Zentralbl. f. Hals-, Nasen- u. Ohrenh., **22**, 204, 1933.
23. Moulonguet, A., and Pierre: Ann. d'oto-laryngol., **2**, 190, 1933.
24. Vail, H. H.: Arch. Otolaryngol., **17**, 212, 1933.
25. Rollin, H.: Arch. f. Ohren-, Nasen- u. Kehlkopfh., **137**, 333, 1933.
26. Fowler, E. P.: J. Am. Med. Assn., **102**, 1651, 1934.
27. Sussman, M. L.: Am. J. Roentgenol., **30**, 415, 1933.
28. Epstein, H.: Arch. f. Ohren-, Nasen- u. Kehlkopfh., **135**, 351, 1933.
29. Taylor, H. K.: Am. J. Roentgenol., **30**, 156, 1933; Arch. Otolaryngol., **18**, 458, 1933.
30. Voss, O.: Acta oto-laryngol., **15**, 469, 1931.
31. Frenckner, P.: Ibid., **17**, 97, 1932.
32. Ramadier, J., Guillon, H., and Becker: Ann. d'anat. path., **19**, 597, 1932.
33. Eagleton, W. P.: Trans. Am. Laryng. Rhin. and Otol. Soc., p. 338, 1930; Arch. Otolaryngol., **13**, 386, 1931.
34. Lillie, H. I.: Arch. Otolaryngol., **15**, 692, 1932.
35. Seydell, E. M.: Ann. Otol., Rhinol. and Laryngol., **42**, 455, 1933.
36. Myerson, M. C., Rubin, H. W., and Gilbert, J. G.: Arch. Otolaryngol., **22**, 62, 1935.
37. Myerson, M. C., Rubin, H. W., and Gilbert, J. G.: Ibid., **21**, 677, 1935.

(Titles have been omitted for sake of brevity.)

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF OCTOBER 21, 1935.

The Water of Serum and the Calculation of the Molality of a Solute in Serum From the Measurement of the Specific Gravity.—FREDERICK WILLIAM SUNDERMAN (John Herr Musser Department of Research Medicine, University of Pennsylvania). Recent studies have demonstrated the desirability in certain instances of expressing the concentration of a solute in serum in relation to the concentration of water. For this relationship the measurements of both the specific gravity and the amount of total solids have been necessary. A linear correlation has been demonstrated between the specific gravity and the total solids of serum so that having determined either of these two measurements a solute measured in relation to volume may be calculated in relation to the water within an accuracy of $\pm 1\%$. In addition the concentration of the water or of the total solids present in serum may be derived directly from the measurement of the specific gravity.

The Fate of Hemoglobin Injected Into the Blood Stream.—David L. Drabkin, A. H. Widerman and H. Landow (Laboratory of Physiological Chemistry, University of Pennsylvania). Small samples of hemolyzed, washed blood cells, containing 0.1 to 0.4 mM. of hemoglobin, were injected intravenously into the same dogs from which the blood was obtained. The fate of the injected blood pigment was followed during the first 20 hours by periodic examination of the serum and of the urine.

By means of spectrophotometric analysis the following points were established: (1) The pigment which appeared in the urine was unchanged hemoglobin. (2) Upon standing, the hemoglobin in the urine was converted rapidly into methemoglobin. This change was due most probably to the presence of oxidants in the urine. (3) In most of the experiments the hemoglobin which appeared in the urine accounted for only one-tenth of the quantity which disappeared from the serum. (4) During the first 20 minutes after the injection, 20 to 45% of the injected pigment was removed from the serum. There appeared to be an inverse relationship between the magnitude of the early loss from the serum and the total hemoglobin which was excreted in the urine. (5) Within 8 hours after injection 90% of the hemoglobin had disappeared from the serum. When HbO_2 was injected neither methemoglobin nor bile pigments could be demonstrated in the serum during the course of the experiments. (6) Injected methemoglobin disappeared from serum at the same rate as injected HbO_2. Some evidence of alteration in pigment, perhaps to a hematin-like substance, was obtained after the injection of methemoglobin. (7) Splenectomy produced no demonstrable effect upon the rate of removal from serum of injected HbO_2.

The Absorption of Cystin, Methionin and Cysteic Acid From Intestinal Loops of Dogs.—James C. Andrews, Charles G. Johnston and Kathleen C. Andrews (Laboratories of Physiological Chemistry and Research Surgery, University of Pennsylvania). The relative rates of absorption of cystin, methionin and cysteic acid have been measured in a dog with an isolated intestinal loop with the result that methionin appears to be absorbed about three times as rapidly as cystin, while the rate of absorption of cysteic acid is intermediate between the two. Since the dog employed for these experiments is the same one which was used over 2 years ago in measuring the rates of absorption of cystin and cysteic acid, we have been able to determine the change in the rates of absorption of these two compounds over that length of time. We found that for both compounds the rate of absorption has decreased to about one-third its original value. The rate of absorption is not a linear relation. In a 6-hour experiment the amount of cystin absorbed is two or more times as great as in a 4-hour experiment. The amount of the amino acid absorbed in a given length of time varies somewhat with the amount placed in the loop: the larger the dose the more is absorbed. The amount of the amino acid absorbed is independent of whether it is administered as the free ampholyte or as the sodium salt.

The amount of the base absorbed from the salt is sufficiently specific and independent of the amino acid with which it is combined as to suggest that its absorption is an independent process when the salt is

capable of hydrolysis (cystin and methionin) but is not independent in the case of the sodium salt of cysteic acid where the salt is incapable of hydrolysis. In this latter case the salt appears to be absorbed as such in equimolar amounts of base and acid.

The Effect of Intense Sound Waves on Some Biologically Important Chemical Reactions.—Leslie A. Chambers (Johnson Foundation for Medical Physics and the Department of Pediatrics, University of Pennsylvania). The most characteristic manifestations of the action of sound on living cells are loss of motility, plasmolysis, vacuolation and disintegration in the order stated. While the lethal action is most pronounced in the presence of cavitation, it also proceeds under pressures which inhibit the formation of cavities in the supporting medium.

In order to explain the biologic action the response of certain simple chemical systems to vibration has been studied. Among the reactions accelerated or induced by audible sound are oxidation of halides, oxidation of H_2O, hydrolyses, depolymerizations and protein denaturation. No reaction has been found to be affected in absence of cavitation.

Protein denaturation by sound requires the presence of certain specific dissolved gases and does not occur in the presence of certain others. Therefore the reaction may not be attributed to kinetic energy increments due to local degradation of acoustic energy.

Furthermore, the specificity of the denaturation reaction toward certain gases indicates a type of energy transfer quite unusual. The unexpectedness of the energy relationships is still further emphasized by the fact that light is emitted from pure water and other liquids during intense vibration.

Complete explanation of the biologic action of sound must await knowledge of these unorthodox energy transfers. However, the observations indicate that intense acoustic fields may be of great value as an experimental tool in both physical and physiological chemistry.

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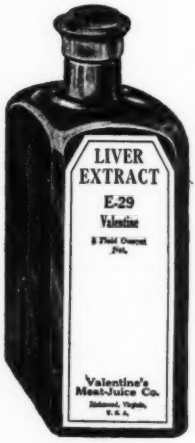

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Of further interest is the paper by Ruffin and Smith entitled, "The Treatment of Pellagra with Certain Preparations of Liver" in the April, 1934, issue of *This Journal.*

[1] Science, 73, 243 (1931)
[2] Jour. Nutrition, 6, 179 (1933)
[3] Klin. Wochschr., 12, 1241 (1933)
[4] Science, 78, 609 (1933)
[5] Va. Med. Monthly, Jan. (1931)

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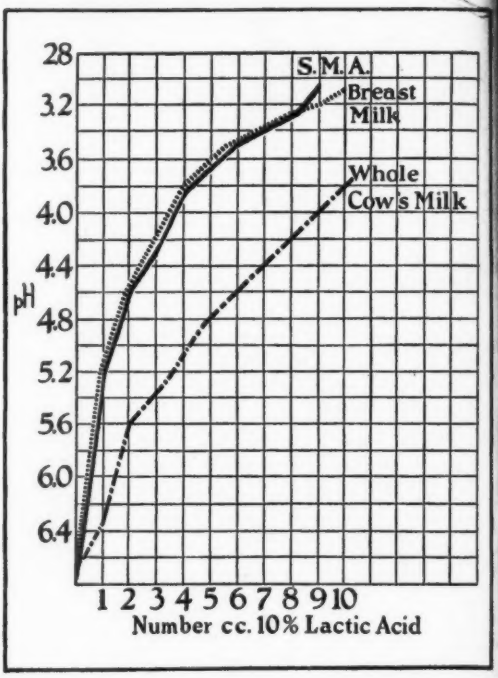

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